# Evaluating and expanding knowledge and awareness of health professionals on the consumption and adverse consequences of Novel Psychoactive Substances (NPS) through innovative information technologic tools

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**Abstract**

**Background**: The rapid diffusion of Novel Psychoactive Substances (NPS) constitutes an important challenge in terms of public health and a novelty in clinical settings, where these compounds may lead to erratic symptoms, unascertained effects and multi-intoxication scenarios, especially in emergency situations. The number of NPS available on the illicit drug market is astonishing: official reports suggest the appearance of a new drug every week. NPS may be enlisted in many different families such as synthetic phenethylamines, tryptamines, cathinones, piperazines, ketamine-like compounds, cannabimimetics and other plant-derived, medical products and derivatives. Therefore, healthcare services and professionals are often called to face this unknown "galaxy" where NPS users seem to perceive traditional services "unfitting" for their needs, requiring an attention which is quite different from known classic drug abusers. In this context, the Recreational Drugs' European Network (ReDNet), a research project funded the European Commission and led by the University of Hertfordshire, aimed to explore the NPS galaxy and develop information tools for vulnerable individuals and professionals working with them. This initiative reported specific Technical Folders on new drugs and disseminated the collected information through innovative communication technologies (e.g. multimedia tools, social networking and mobile phone services) internationally.

**Aim and objectives**: The aim of this work is to evaluate and contribute to expand the knowledge of health professionals on NPS. The key objectives are: 1) to assess the level of knowledge on NPS amongst a sample of Italian healthcare professionals; 2) to evaluate the effectiveness of dissemination tools developed by ReDNet, including an SMS-Email/mobile service (SMAIL); 3) to understand the clinical impact of NPS by providing four Technical Folders and collecting two clinical cases on NPS.

**Methodology**: According to the objectives, the methodological approach has been articulated in the following three phases. *Phase 1*: investigating knowledge and preferred channels of information via an online survey among health professionals in Italy. This first Italian study on NPS awareness had been online from February to July 2011, recruiting participants from Departments of Addiction, Psychiatry and other services. *Phase 2*: evaluating the ReDNet initiative. An evaluation questionnaire was designed and disseminated online to assess the various resources provided by ReDNet project; it had been online from April to July 2013, targeting professionals registered to ReDNet services. This phase also investigated the SMAIL service, a mobile application that was the latest technological tool developed by ReDNet team. *Phase 3*: promoting evidence based work in clinical practice through the preparation of four Technical Folders and two case reports. Technical Folders followed the methodology optimised during the ReDNet experience, organising NPS data under specific headings, measured for the need of health professionals. Case reports were collected in a Dual Diagnosis Unit in Italy ("*Casa di Cura Parco dei Tigli"*); assessed patients revealed for the first time the use of NPS; clinical interviews were conducted to collect a full anamnesis while for the first time psychopathological characteristics were measured in NPS abusers, using a psychometric instrument (MMPI-2).

**Results**: In *Phase 1* Italian services, in particular interviewees (n=243) from Departments of Psychiatry and Addiction, showed a strong interest for the subject but a poor understanding of NPS: 26.7% of respondents did not know if their patients ever used NPS; at the same time they considered this phenomenon as very relevant to their profession (e.g. psychomotor agitation [75.7%], errors in the assessment [75.7%], management of the clients [72%]); in addition less of a quarter of them had reliable information on new substances. Interviewees also reported the need for easily accessible channels of information to expand their expertise in the field (including emails [70%] and dedicated websites [51.9%]). The ReDNet initiative (*Phase 2*) reached professionals (n=270) from European countries and various other regions; they appreciated the website above all (48.5%), which provided access to other information (in form of academic papers, news, technical folders, etc.). The integration of technological-based and classic educational resources was used to self-educate professionals (52.6%) and supply information for research (33.7%) with up-to-date and

reliable information; in the same *Phase* the SMAIL service was analysed in its first 557 searches: in the pilot period 122 professionals used SMS inquiries (95%), asking information on NPS while highlighting the increasing number of NPS available on the market. Technical folders (*Phase 3*) described two new phenethylamines (Bromo-dragonfly and 25I-NBOMe), a novel ethno drug (Kratom) and a new synthetic cathinone (alpha-PVP) whose severe effects were also described in one of the clinical cases. The first case report (*Alice*) involved a clubber who used mephedrone and other NPS with a severe worsening of her psychiatric disturbances; the second one (*Marvin*) described a patient who was referred by a psychiatric service and revealed himself as a "psychonaut" with an intense abuse of alpha-PVP.

**Conclusions**: The exploration of the NPS galaxy is a new challenge for healthcare professionals. In this study, Italian services seemed to be unprepared to face the emergency and requested rapid access to reliable information; the ReDNet project provided both technology-based and traditional resources to expand knowledge on NPS, making professionals more aware of emerging issues and helping especially clinicians working in the field (e.g. via SMAIL service and Technical Folders). Overall, it can be observed that effective information services on NPS targeted at professionals initiatives should include an online interface integrating up-to-date information, describing NPS through specific Technical Folders and disseminating scientific literature; the use of technological tools, including mobile applications, is an important strategy to support health professionals in their activity. Finally, more "visual" guidelines, possibly in the form of a "map" of these heterogeneous compounds, could be a useful framework to describe NPS to physicians and other professionals who are often unprepared and unconfident to face such an expanding galaxy.

## TITLE

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## BACKGROUND

### Novel Psychoactive Substances (NPS)

Novel psychoactive substances (NPS) comprise an increasing number of "designer", pharmaceutical and herbal drugs[1], often advertised and sold as 'legal' alternatives to illicit drugs[2-7]. The term has been formally defined by the European Union as "a new narcotic or psychotropic drug, in pure form or in a preparation, that is not scheduled under the Single Convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971[8], but which may pose a public health threat comparable to that posed by substances listed in those conventions (Council of the European Union decision 2005/387/JHA)"[1].
The rapid diffusion of NPS represents a novel phenomenon in which synthetic drugs can be re-invented, re-introduced and experimented in their effects. Even if NPS can be cataloged in many ways (e.g. chemical structures, effects, etc.), the following groups of substances have been identified by EMCDDA on the basis of that definition and recently enlisted as the main NPS families[9]:

- Phenethylamines: which encompass a wide range of substances that may exhibit stimulant, entactogenic or hallucinogenic effects (e.g. 2C compounds, 25NBOMe group).
- Tryptamines: which include a number of substances that have predominantly hallucinogenic effects (e.g. 5-Meo-DALT, 5-MeO-DMT)
- Synthetic cathinones: which have stimulant effects derived by cathinone structure (e.g. methcathinone, mephedrone, methylone and MDPV)
- Piperazines: which are central nervous system stimulants (e.g. benzilpiperazine)
- Synthetic cannabinoids: they are functionally similar to THC, the active compound of cannabis (e.g. JHW compounds)
- Ketamine and phencyclidine (PCP) like compounds: chemically derived from these dissociative drugs (e.g. methoxetamine)
- Other substances reported to the early warning system (EWS) which do not strictly belong to any the above mentioned drug families, like various plant-derived and synthetic psychoactive substances and a number of medicinal products and derivatives (e.g. prescribed medicine, narcotic analgesics or synthetic cocaine derivatives)

The amount of these novel compounds appeared on the illicit drug market is astonishing: in the European Union the EWS reported the appearance of more than one new NPS on the market every week [4,10]. These new products are sold online, even with periodic discounts and offers, using new brand names to attract customers and young people with aggressive marketing strategies.

Overall more than 750 new substances and combinations were identified by regular online monitoring at the Recreational Drugs European Network (ReDNet)[5] and some of these results will be presented and discussed in this thesis. Such an expanding "galaxy" will be here presented in terms of a) its definition, b) its "cyber-size" diffusion, c) its main "constellations" in term of NPS classes, d) the risk of health professionals as unprepared "explorers".

### The lack of information of NPS: the unpredictable impact on public health and the challenge for health professionals

#### *NPS and their ambiguous definitions*

As outlined above, the emergence of NPS on the world drug scene represents a fast growing phenomenon with an incredible pace over the last decade [7,11]. This has posed a real challenge for health professionals who should be aware of the nature and problems associated with the consumption of these new drugs and appropriately be equipped to deal with largely unknown synthetic substances.
The terminologies used to define these drugs is often itself a problem (Table 1).

Table 1: Alternative and different definitions of novel substances.

| |
|---|
| **Legal highs** |
| **Designer drugs** |
| **Research chemicals** |
| **Analogue compounds** |
| **Mimetic compounds** |
| **Performance and Image Enhancing Drugs (PIEDs)** |

As illustrated in Table 1 in fact, these novel compounds have been given different and sometimes misguiding names; therefore mental health professionals may be confused about these different names adopted in several contexts. Here are the most important and common used names:

- ***Legal highs***: it is an umbrella and misleading term[12] even if quite popular in scientific literature. The term encompasses novel compounds, which are online offered as "legal" drugs (emphasizing the idea of legality), "research chemicals" (implying a sort of legitimate research use), "party pills" (describing them new "party drugs") and "herbal highs" (stressing the plant and natural origin even if they are synthetics). Therefore "legal highs" comprises a) a wide range of compounds and products, both synthetic and/or plant-derived substances b) substances which are frequently sold via the Internet or in "smart shops" (also called "head shops") c) compounds in many cases that are intentionally mislabeled, with purported ingredients differing from the actual composition. Under this term there are a number of new and non-controlled - synthetic substances emerging every year on drug and online markets. In the past decade with this name gained popularity mephedrone and the synthetic cannabinoids, and also BZP and many other drugs. In addition, according to this definition many other plant-based substances gained huge popularity in the new millennium, including a plant like Kratom (*Mitragyna speciosa*, grown in South-East Asia, sold as a mild stimulant that interacts with the opiate receptors, as sedative at higher doses [see the Technical Folder in Phase 3]), *Salvia divinorum*, a powerful hallucinogen grown in Mexico, Piper methysticum (known as "Kava Kava"), Ayahuasca (a South American brew with psychedelic effects) and Ibogaine.
  For instance, substances sold as "legal highs" are mainly manufactured in chemical laboratories located in Asia, according to the International Narcotics Control Board and the European Police Office (Europol), although some manufacture also takes place in Europe and other regions, including the Americas. They are "legally" imported thanks to their status and are sold and advertised either as chemicals or as packaged products. Typically suppliers circumvent drug controls by offering new alternatives to restricted products, adopting aggressive and sophisticated marketing strategies: "legal highs" are sold as air fresheners, herbal incenses, bath salts, plant fertilizers, collectors' items[13-17]. As a matter of fact, the term "legal high" can be described as a successful and worldwide marketing instrument in and of itself: it suggests that these substances are not as dangerous as controlled drugs, with the result of increasing their popularity and sales, even if compounds presented as "legal highs" often also include drugs controlled in some countries, for example as contaminants[18]. According to Oxford Dictionaries Online (Oxford Dictionaries. Available from http://oxforddictionaries.com/) a "legal high" is considered a substance "whose sale or use is not banned by current [national] legislation" which means that by controlling a substance under the national drug laws, such a compound ceases to be a "legal high". Thus there is a legislative inconsistency across different jurisdictions: as many substances are under control such compounds are in fact no longer "legal highs" in those countries, while continuing to be "legal highs" in others. The result is when legislators discuss it about a compound it can be legal in a country and banned in another.
- ***Designer drugs***: this term defines substances synthetically designed. According to the International Narcotics Control Board the "designer drugs" are "substances that have been developed especially to avoid existing drug control measures ⋯ [and] are manufactured by

making a minor modification" to the molecular structure of controlled substances, resulting in new substances with pharmacological effects similar to those of the controlled substances[19]. Similarly the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the European Police Office (Europol)[2,4,20] defined them as compounds designed to mimic the effects of controlled drugs by slightly altering their chemical structure in order to circumvent existing controls. An important observation is that the term is not a novelty itself: it was coined early in the 1980s referring to various synthetic opioids, mostly based on modifications of fentanyl (e.g. alpha-methylfentanyl), but the term entered widespread use when MDMA ("ecstasy") experienced a boom in the mid-1980s. Once ecstasy was scheduled (in the United States in May 1985 and a year later at global level), a number of chemically related substances appeared on the drug markets, and they were labeled as "designer drugs" because they were related to MDMA but fell outside the drug control system.

There are many examples of these group banned in different years:

- ✓ methylenedioxyamphetamine (MDA) and methylenedioxyethylamphetamine (MDE) got scheduled at the international level in 1990;
- ✓ *alpha*- Ethytryptamine (AET) was placed under control in 1993;
- ✓ *alpha*-Methyl-4-methylthiophenethylamine (4-MTA) and 4-bromo-2,5-dimethoxyphenethylamine (2C-B), one of the designer drugs first synthesized by Alexander Shulgin in the 1970s, were scheduled in 2000s.

So again, if we consider this definition, the term "designer drug" is not suitable for substances already under control; nonetheless, the usage of the term persisted, although it was later replaced by the term "club drugs" [21] which refers to substances used by teenagers and young adults at bars, nightclubs, concerts and parties. According to the United States National Institute on Drug Abuse[22], such "club drugs" include "ecstasy" and related substances, but also methamphetamines, gamma-hydroxybutyric acid (GHB), flunitrazepam (Rohypnol)[23].

Therefore the term "designer drugs" includes many different groups of substances, classically a) derived from others compounds b) with modifications in their structure while the term "club drugs" can be described with similar properties but the term want to emphasise the social environment where these compounds are used, mostly to increase empathy amongst users.

- ***Research chemicals***: this definition indicates compounds branded as "not for human consumption". The term seems to be coined by marketers and online sellers of designer drugs and "legal highs", specifically, marketers of psychedelic drugs (i.e. drugs with hallucinogenic properties) and in particular in the tryptamine and phenethylamine families, which are two important classes of compounds. Again the intent here is to avoid laws selling compounds intended to a "scientific" purpose instead to recreational human use: it seems to be a common strategy in the NPS world, where substances are dispatched as "something else". For example cathinone-related compounds became famous and popular, even in media descriptions, as "bath salts" labeled as "not intended for human consumption".
- ***Analogue compounds***: an analogue drug is a structural derivative with chemical modifications. Again, it's not a novelty: in the work of the Shulgins most phenethylamines and tryptamines are described as analogues of a limited number of substances. The important point here is that an analogue, even though very similar chemically, may not have the same pharmacological properties as the original compound: MDMA, commonly known as "ecstasy", is an analogue of methamphetamine, although the pharmacological properties of the two are quite distinct; or for what concerns NPS the cases of methoxetamine[24-27], synthetic cathinones[28] and cannabinoids[29,30]. As some authors in literature suggested recently it could be an important "lesson from the past"[31], because as researchers and clinicians we may foresee some effects of analogue drugs in term of medical and psychopathological risk but at the same time we could expect uncertain, unpredictable and dangerous (side) effects.
- ***Mimetic substances***: they are substances that are able to a mimic specific pharmacological effect. Examples are synthetic cannabinoids (ingredients of "Spice drugs"[13,32]): they act as

mimetics of THC (tetrahydrocannabinol), the main psychoactive substance in cannabis; such substances act on the same cannabinoid receptors as does THC producing effects similar to those produced by cannabis. But a mimetic compound does not simply interact with the same receptor, as a matter of fact nowadays we know that the effects depends on properties of affinity and avidity, not only on the interaction with it and that is the reason why synthetic cannabimimetics differ from each other and produce unpredictable symptoms in users[30,33]. Again, these products are synthetic drugs designed to circumvent controls and over the years, Governments have developed various approaches to deal with such a phenomenon.[7,11]

- ***PIEDs*** (Performance and Image Enhancing Drugs). This term refers to different groups of substances, including drugs, drinks and nutrients used with the purpose of increasing performance or appearance[34]. Originally the acronym "Performance-Enhancing Drugs" (PEDs) was the first term used to describe the range of substances that could have performance benefits only for athletes[35,36], while Performance and Image Enhancing Drugs (PIEDs) indicate in general compounds that are a) used to enhance muscle growth (anabolic effects), B) to reduce body fat (catabolic effects), c) to increase cognitive functions d) to enhance sexual performances[37] e) to improve aesthetic appearance in general. So the consumption of these compounds seems to involve different populations[38], not just sporting community, with an easy access through online websites to many substances. Classically, literature[35] identifies four general categories of non medical users of PIEDs:
  - elite athletes,
  - body image users (including people affected by body dismorfic disorder [BDD])
  - occupational users (works where the survival depends on physical abilities [e.g. police, bodyguards, members of armed forces] or/and aggressive levels [e.g. street gangs; criminal or anti-social activities]
  - adolescents.

  The expected benefits of using these types of substances range from increasing the size and definition of muscles, reducing water retention and body fat, to increasing physical strength and endurance, but also aggression levels. The main aim is to obtain social acceptance, admiration and opportunity. Use of PIEDs often occurs without any kind of medical supervision, even if prescribed drugs and their amounts are greatly exceeded than the recommended therapeutic doses. As a matter of fact, assessing the health risks can be difficult as users often take a complex combination of drugs. Many of the substances used are obtained and used illicitly, and there is an active black market for PIEDs. This group includes for example:

  - ✓ human and veterinary anabolic- androgenic steroids (AAS),
  - ✓ growth hormone,
  - ✓ other reproductive hormones,
  - ✓ diuretics,
  - ✓ stimulants,
  - ✓ beta-2 agonists,
  - ✓ creatine monohydrate,
  - ✓ insulin,
  - ✓ thyroxine.

In the last few years this heterogeneous group has been enlisted in the NPS family[34,39] because it shares many of their features, like the perceived 'legal status', availability online, accepted as part of a lifestyle and being sold online without a medical prescription. So many NPS are sold and used as PIEDS, for example:

- ✓ Melanotan synthetic tanning agents;
- ✓ Ethno-drugs or herbal products (e.g. Tribulus terrestris);

- ✓ Cognitive enhancers[34] (e.g. aniracetam, piracetam);
- ✓ Sexual enhancers[37], including natural products (e.g. yohimbine, Maca, Epimedium and Ginkgo Biloba) and prescribed drugs;
- ✓ Stimulants (mostly phenethylamines), also contained in dietary supplements with amphetamine –like effects.

There is obviously an overlapping area between these different definitions ("legal highs", designer drugs, research chemicals, analogues and mimetic compounds, PIEDs) even if all these substances are heterogeneous in terms of chemical group, desired effects, consumptions, medical risks and psychopathological disturbances. During the last decade there has been a sharp change in the social, cultural, legal and political context of drug addiction, which has led to unprecedented new challenges, especially with accessibility to the internet: it has been documented that an increasing number of unregulated websites are dedicated to the dissemination of novel herbal, 'designer' and pharmaceutical psychoactive drugs, and so the first element in common between all NPS is the availability on the online market[18,40-51]. Effectively these new substances are widely distributed on the Internet, and can be bought by anyone with a credit card and a shipping address, without any kind of prescription: information regarding safety content, interactions, and side-effects is seldom provided and reliable information regarding long-term effects, toxicity, and abuse potential are mostly missing as well. Many of these drugs are also unfamiliar to clinicians and health care providers or their consumption as recreational drugs is unknown[52-54].
Another evidence is that NPS seem to be attractive to young people: several studies indicate that the prevalence of "legal high" drug use is highest among youths, more specifically in the group of males aged 16 to 25[44,55,56]: typically these drugs are of particular concern as they are advertised as 'legal' , 'natural', 'safe' and 'pure', making them attractive to users mainly of the teenage group.

**Table 2: Key points about NPS.**

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| **Not approved for human consumption with unknown pharmacological effects, unpredictable side effects and adverse reactions on users** |
| **Legal and thus perceived as 'safe' by users/potential users** |
| **Often sold as something else, like mystical incenses, plant chemicals and bath salts** |
| **Unknown to health and other professionals who constantly need to receive updated and accurate information about these new substances.** |
| **Not mentioned in the scientific literature, generally restricted to studies in animals** |
| **Are increasingly accepted as part of a lifestyle rather than being considered as a misuse of drugs** |
| **Are just a 'click away' and thus potentially available to everyone, especially young people who are amongst the most at risk in taking advantage of information and products available online** |
| **If medical product they are not consumed at prescribed dosage or through standard way of intake.** |

### *The term NPS: finding an appropriate definition*

As it has been suggested[12], the most appropriate term to refer to these substances is NPS or NPD (Novel Psychoactive Drugs). Both terms are more appropriate definitions, internationally understood and easily translated in different languages. Terms as "legal highs", largely used by media, should be avoided in scientific literature and preventive interventions: labelling this compounds as "legal" is misleading to users, contributes to their marketing strategies and distorts the perception of health risks.
The use of the term NPS to better define these groups of substances and to serve policymaking at regional and international levels has also been encouraged in official reports by the Advisory Council on the Misuse of Drugs (ACMD)[1], EMCDDA[2,10] and the Commission on Narcotic Drugs[57]; however the term remains still relatively new and unfamiliar for most of the professionals, requiring additional prevention and informative services.
In truth, many NPS are not completely "unknown": their use constitutes a novelty, so as stated in the EMCDDA operating guidelines [58] "the term 'new' did not refer to newly invented, but rather "newly misused" substances as most of the drugs in question were first created many years ago". In fact,

they only started to emerge as a health problem in the decade 2001-2010 in several countries: for example mephedrone was first synthesized in 1929 but was rediscovered only in 2003 and reached the markets towards the end of the decade 2001-2010[20,28,59-63]. Similarly many herbs/plants enlisted by EMCDDA have been known for hundreds of years in different countries and cultures (with divinatory intent or in shamanic rituals, for example) but their consumption in modern civilization and their spread through the internet is a novelty: for example khat (*Catha edulis*) is a popular plant around the Horn of Africa and the southern parts of the Arabian peninsula, used as a stimulant because of the properties of its alkaloid (cathinone)[64,65]. However, it is considered to be a new substance and it was recently banned in a number of European and American countries: its use was barely known in those regions until one or two decades ago. Other similar plants, considered NPS because their emergences in the online market, are: *Salvia divinorum*, Kratom (*Mitragyna speciosa*), Ayahuasca, ibogaine, "kava kava", many other herbs, and various hallucinogenic mushrooms.

Therefore another important point here is that NPS could be drugs "newly misused on the market": we can describe their specific geographical origin, but will always be some countries in which they have not been misused before, resulting not "illegally" consumed.

***NPS spread as an international phenomenon***

According to international reports compiled in the last few years[3,4,10,20,58,66,67] the use of new psychoactive substances (NPS) is a global emergency: the number of NPS on the global market more than doubled over the period 2009-2013[57], spreading all over the world (Figure 1). According with the UNOCD[7,57] new psychoactive substances can be found in most of Europe and North America, as well as Oceania, Asia and South America and in a number of African countries, too (Figure 2). Of 103 countries for which information on new psychoactive substances was available (December 2013), 94 countries reported the emergence of such substances on their markets, up from 70 out of a total of 80 countries as of July 2012.

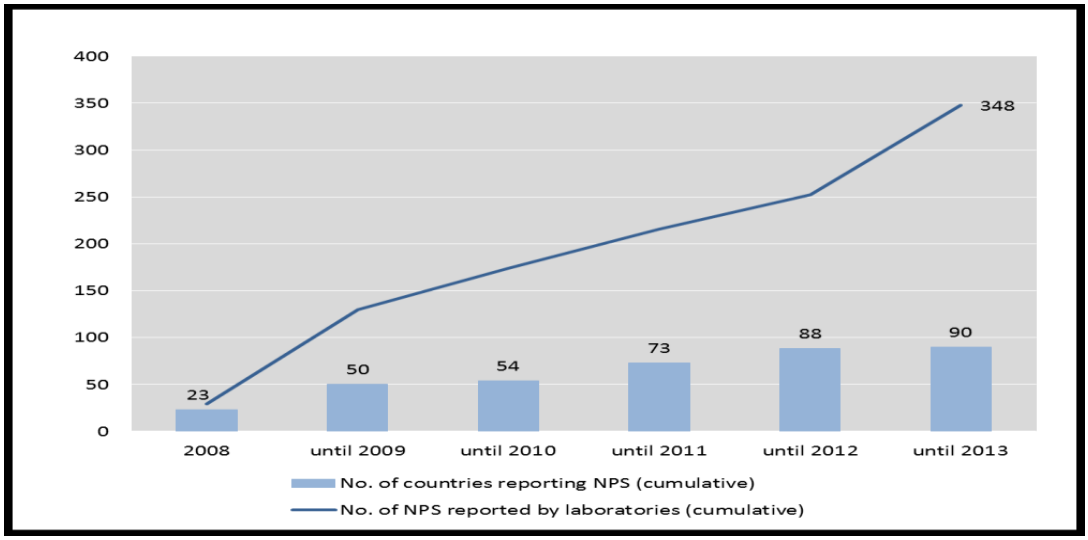



**Figure 1: The increasing number of reported NPS (Source: UNODC, 2013).**

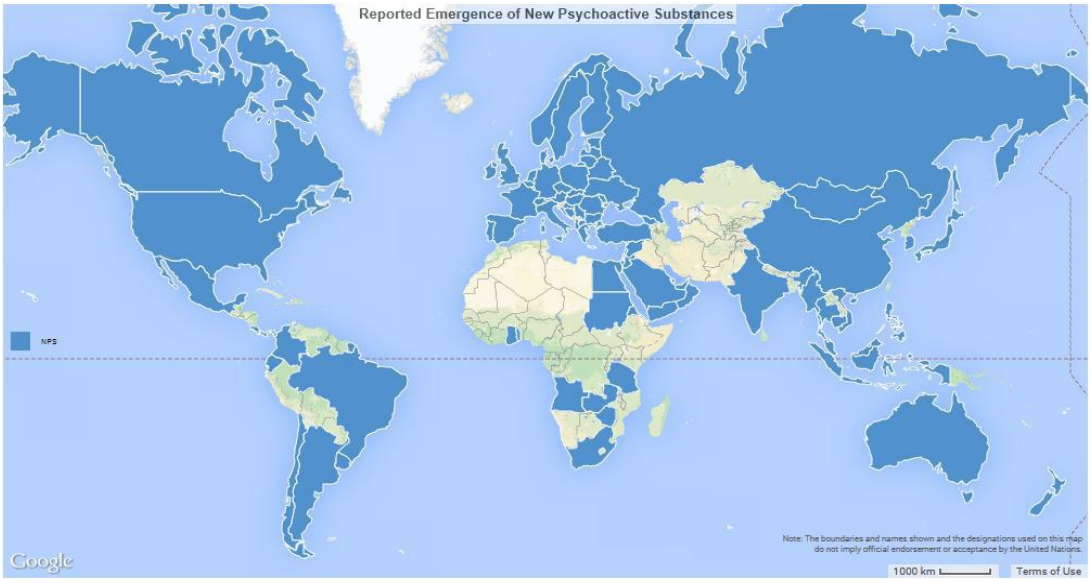



**Figure 2: Worldwide reported NPS (Source: UNODC, 2013).**

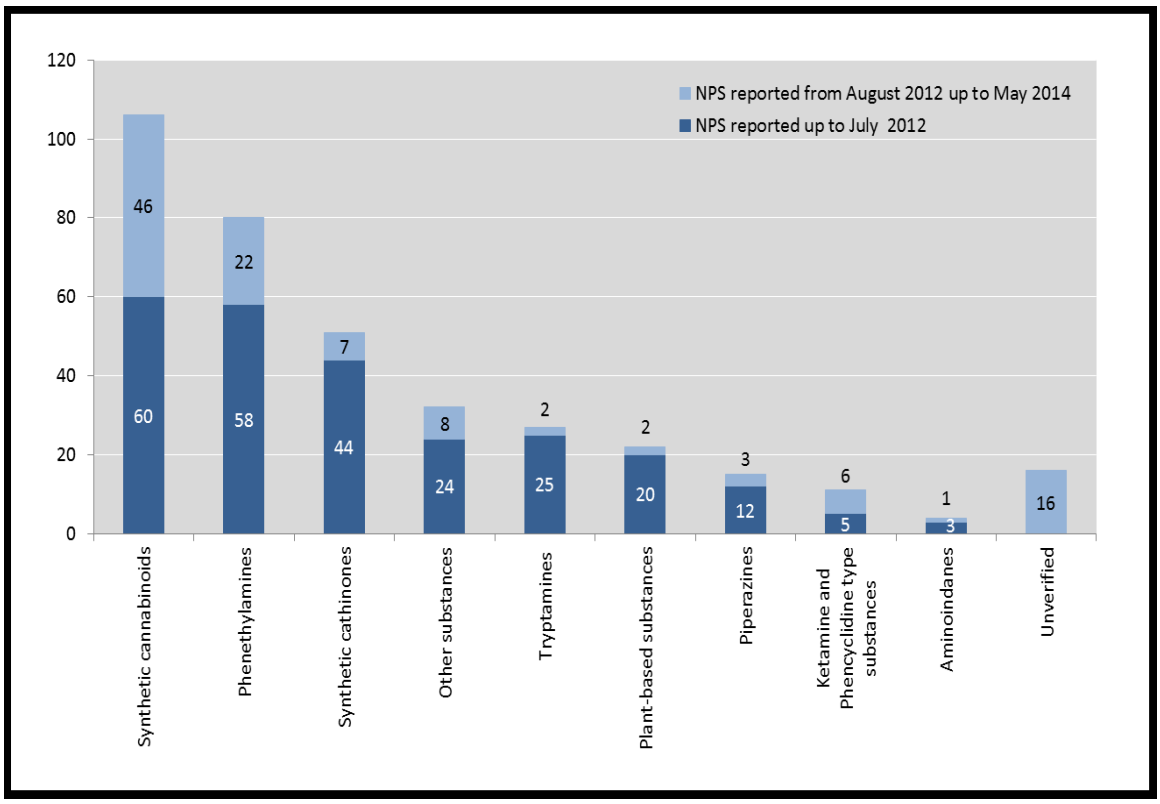



**Figure 3: Reported NPS up to May 2014 (Source: UNODC, 2014).**

This upward trend in seizures, in addition, reflects the increasing number of substances that have been scheduled in recent years in various countries. The number of novel compounds is astonishing: a total of 251 NPS (including ketamine) were reported to UNODC by 40 countries and territories up to 2012, and just in 2013[4] 81 novel compounds has been notified by Member States for the first time through the EU Early Warning System[68] (EWS). In countries of the European Union the EWS monitors the emergence of NPS, reviewing new substances reported by Member States of the European Union (Figure 3). The increasing trend over years confirms the idea of a "expanding" galaxy

phenomenon: the number of substances has continuously increased, whereas in 2009 only 24 substances were reported, 41 were formally notified in 2010, 49 in 2011 and 73 NPS reported in 2012[4,10,66]. In terms of groups, about two thirds of the newly notified substances reported were synthetic cannabinoids or synthetic cathinones. Specifically in European countries considering 2009 and 2012 out of the new reported NPS there are synthetic cannabinoids (60 substances), followed by phenethylamines (58 substances) and synthetic cathinones (44 substances) and at the global level, most reports pertaining to NPS concern synthetic cathinones, with 684 reports, followed by synthetic cannabinoids with 665 reports.
However, the extent of global use of NPS remains unknown[57]. Thus far, there are no estimates on the prevalence of use of NPS in the general population, but rather limited data collected in few countries, with respect to specific substances and subpopulations, in particular young people.

Overall, the more recent 2015 European Drug Report (www.emcdda.europa.eu/publications/edr/trends-developments/2015) highlighted the increasing seizures of new drugs and the growing number of new substances detected in Europe: thirty-one were in the class of synthetic cathinones, thirty were synthetic cannabinoids and thirteen were did not fit in any group. The EMCDDA specifically risk-assessed six new NPS only in 2014 (4,4-DMAR, MT-45, 25I-NBOMe, AH-7921, MDPV and methoxetamine) as EU mechanism for the identification, assessment and possible control of new substances which emerged in the past years and were linked to a growing number of reports of harm. The agency underlined also the role of Internet in form of online marketplace and cryptomarkets (e.g. Silk Road) accessible with encryption software.

Similar data were confirmed by the 2015 World Drug Report (www.unodc.org/wdr2015), which specified that comparison of prevalence of use trends of NPS and other drugs were limited (e.g. cannabis vs synthetic cannabinoids). The majority of countries and territories that reported the emergences of NPS up to December 2014 were from Europe (39), Asia (27), Africa (14), the Americas (13) and Oceania (2), with 69 substances reported to the advisory for the first time. Synthetic cannabinoids (39%), phenethylamines (18%) and synthetic cathinones (15%) were more worldwide identified class of compounds in 2014, even if many NPS were found to be transient in their appearance, disappearing as quickly as they materialize.

In the framework of the European Union, the attitude of youth towards drugs is regularly examined by the Eurobarometer, which analyses public opinion in Member States of the European Union[69] using a survey conducted amongst young people. These surveys have studied the attitude of young people toward licit and illicit substances including heroin, cocaine, ecstasy, cannabis, alcohol and tobacco. In 2014 results of Eurobarometer specifically suggested:

- Increasing percentage of young adults who used NPS (from 5% to 8% comparing data of 2011)
- NPS users consumed these compounds at parties or events (65%), with friends (60%) and also in 9% of cases during normal activities.
- 47% of respondents thought that NPS should be banned only if they pose a public health treat.
- The Internet is the most-mentioned source of information on drug use.
- Young people were most likely to have received information on new substances that imitate the effects of illicit drugs from the Internet (30%), media campaigns (29%), school prevention programs (22%), or friends (18%).
- In the past year 29% of young people were not informed at all about new substances.

In addition to the European study mentioned above, national surveys among general population and/or subpopulations have also been conducted in some countries. However, these were less comprehensive and limited to a few NPS. For example in Australia, questions on the prevalence of

use of NPS has been included in national survey Drug Trends in Ecstasy and Related Drug Markets (EDRS) report since 2010[70] : a increasing number of regular ecstasy users reported the use of some NPS (synthetic cannabinoids, synthetic cathinones [mephedrone, methylone, MDPV], phenethylamines [2C-I, 2C-E, 2,5-dimethoxy-4-iodoamphetamine (DOI)], piperazines (BZP), tryptamines and plant based substances (*Datura stramonium, Salvia divinorum*). Data collected in the last report (2013) estimated a steadily increasing presence of NPS, especially synthetic cannabis but also mescaline, 2C-I, 2C-B and mephedrone. In Canada, the use of NPS was recently included in the biennial Youth Smoking Survey[71] (YSS) conducted since 2002. The YSS helps schools and government agencies across Canada assess youth substances use and related health behaviors: survey results showed a higher last year prevalence of the use of NPS (*Salvia divinorum;* ketamine and other illicit drug) than for other illicit drugs, such as cocaine and heroin.

In the United Kingdom, new measures of drug use were added to the British Crime Survey (BCS), with the inclusion of novel drugs recently classified under the Misuse of Drugs Act[72]. Considering recent findings (2013/14)[73], collected data suggested an increased consumption of cocaine, MDMA, hallucinogens, stimulant drugs, LSD and ketamine comparing with the previous year. Mephedrone, for example was investigated in 2010/2011 in adults resulting as popular as ecstasy and cocaine; in recent years questions about different compounds such as khat, *Salvia divinorum* and nitros oxide were introduced.

In the United Kingdom, the British electronic dance and clubbing magazine 'MixMag' has conducted three different surveys on NPS, in 2009, 2011 and also in 2013[74]. The survey had been traditionally addressed to young club goers, but over the last few years it has attempted to involve a wider segment of the population. Results are interesting to understand and estimate the phenomenon in UK: the first questionnaire carried out in 2009 collected substantial data (of lifetime, last year and last month drug use) on 29 substances, including NPS such as synthetic cannabinoids, synthetic cathinones, phenethylamines, piperazines, *Salvia divinorum* and 'other new psychoactive substances'. The first results of interest in the 2009 survey was that lifetime and last-month prevalence of other NPS surpassed the use of illicit drugs (e.g. heroin and methamphetamine): ketamine was described as the most common new psychoactive substance (51%), followed by synthetic cathinones (mephedrone 37.3%), piperazines (BZP 12.1%), and, to a lesser extent, plant-based substances (S*alvia divinorum* 8.9%) and synthetic cannabinoids (6.2%). The second Mixmag survey was carried out in 2010, involving a larger population sample, more than 15,500 people worldwide, aged mostly between 18-27, male in two-thirds of cases (69%). Results here showed a higher prevalence of mephedrone (51% in 2010 vs. 37% in 2009), a fall in last year use of ketamine from 2009 to 2010 (50.7% vs. 41.2%). All in all, in 2010 last year use of several NPS such as synthetic cannabinoids (2.2%), MDPV (3%), or BZP (5%) remained higher than last year use of classic drugs of abuse. The last survey (2013) of MixMag[74] described a similar distribution and in particular:

- An increasing percentage of UK respondents who used synthetic cannabinoids (3.3% vs 2.2%) and a greater number of US respondents (14%) who did it in the last year, seeking in many cases medical help after the consumption due to panic attacks, anxiety or more severe symptoms.
- 14.6% of all sample snorted or ingested a mystery powder, with which they intoxicated themself with it in the 80% of cases.
- A decrease in the use of mephedrone amongst "club users", rating it as the "worst drug" because of the unpleasant comedown.
- Research chemicals were mostly bought on the Internet (53%).

**Table 3: The most used NPS in UK (Source: MixMag survey data 2011-2013).**

| |
|---|
| **Mephedrone** |
| **Synthetic cannabinoids** |
| **Ketamine** |
| **Salvia divinorum** |

| Piperazines |
|---|
| MDPV |

In the United States, the *Monitoring the Future* survey[75] has been conducted annually since 1975: a question about the use of synthetic cannabinoids was included starting from 2011, asking 12th graders about their use in the previous 12 months. The sample size in the 2011 survey encompassed about 46,700 secondary school students and, according to the findings of the survey, synthetic cannabinoids ranked second only to natural cannabis in annual prevalence. Some 11.4% of 12th graders reported having used synthetic cannabinoids in the previous 12 months, while 5.9% of these users reported last year use of *Salvia divinorum*. Also here, according to collected results (2011) the experimentation of NPS among 12th graders surpassed the use of other classic illicit drugs such as cocaine (2.9%) and heroin (0.80%). Among all young adults aged 19-30, the annual prevalence of synthetic cannabinoids was 6.5%, but there were considerable differences by age. With annual prevalence rates in 2011 between 2% and 5%, *Salvia divinorum* seemed to be more widespread among 19-24 years olds than among those aged 25 to 30, where annual prevalence was less than 1%. Most recent results in the 2013 survey detected relevant differences that authors related to legal measures against NPS, in particular:

- Synthetic cannabinoids' users decreased to 6%, probably due to a higher reported perception of danger amongst young people and federal laws that close down the sale of these compounds, previously sold in gas stations, convenience stores and head shops;
- Bath salts declined in use in 2014 probably for the same reasons;
- *Salvia divinorum* use had fallen to quite low levels of use (2%);
- Hallucinogens like psilocybin were continuing a long-term decline;
- Any prescription drug misuse includes use of narcotics, sedatives, tranquilizers, and/or amphetamines without medical supervision showed a substantial increase.
- Other drugs for which use remained unchanged in 2014 include Ritalin and Adderall—both stimulants used in the treatment of ADHD—as well as LSD, inhalants, powder cocaine, tranquilizers, sedatives and anabolic steroids.

**Table 4: The most used NPS amongst US teens (Source: *Monitoring the Future* 2013).**

| Synthetic cannabinoids |
|---|
| Bath salts |
| Salvia divinorum |
| Hallucinogens (other than LSD) |
| Prescription drugs |
| Others |

As previously noted, various control measures on NPS have been taken in the US at national and federal level: in 2011, mephedrone, methylenedioxypyrovalerone (MDPV) and five synthetic cannabinoids were placed under temporary control[76] and then in 2012, these substances, along with 26 synthetic cannabinoids were placed permanently under control within the Controlled Substance Act (as amended by the Synthetic Drug Abuse Prevention Act of 2012[77]). As a result the prevalence of the use of synthetic cannabinoids and of "bath salts" (synthetic cathinones) declined among high school students as described in surveys. A recent report[78] highlighted the situation regarding designer drugs and described as most recently in March 2014, Attorney General Holder—again through the DEA—used his temporary scheduling authority to place 10 synthetic cathinones on Schedule I of the CSA (Controlled Substances Act).

In England and Wales, the Government activities aimed at raising awareness among drug users, and increasing awareness about the health risks associated with NPS (for example, through the Internet

website "Talk to Frank" (www.talktofrank.com), the Welsh Emerging Drugs and Identification of Novel Substances project (www.wedinos.org), the ReDNet project (www.rednetproject.eu), the most recent EuMadness (www.eumadness.eu) and High Wise (www.novelpsychoactivesubstances.org). Similarly to US, legal measures specifically "designed" for NPS proved to be useful: the introduction of national controls took place in the same period and the annual prevalence of mephedrone and synthetic cathinones, fell by more than 60 per cent among those aged 16-24 years in 2010/11 to 1.6 per cent in 2012/13. Hence, legally speaking the UK approach is well described in government reports[79] while from a operative point of view the size of the problem and possible solutions in UK unprepared services are well exposed in a document of the Royal College of Psychiatrists[80].

In other countries the phenomenon is still emerging: for example two recent studies[81,82] revealed through the online monitoring in Persian language websites led to the identification of a number of 14 NPS: herbal, synthetic, pharmaceutical and combination of drugs. These compounds were sold online, concluding that the availability of online marketing of NPS also in Persian language websites may constitute a public health challenge at least across Farsi-speaking countries and so revealing the expansion of regular offer of NPS also in the Middle East.

For what concerns Italy, through an intensive collaboration with the EMCDDA, the DPA (Dipartimento Politiche Antidroga)[83,84] identified almost 300 new compounds in the national territory, including 84 synthetic cannabinoids, 42 synthetic cathinones, 60 phenethylamines, 6 ketamine-like substances, 4 piperazines, 8 tryptamines, 4 PCP-like compounds, 3 phentanyls.

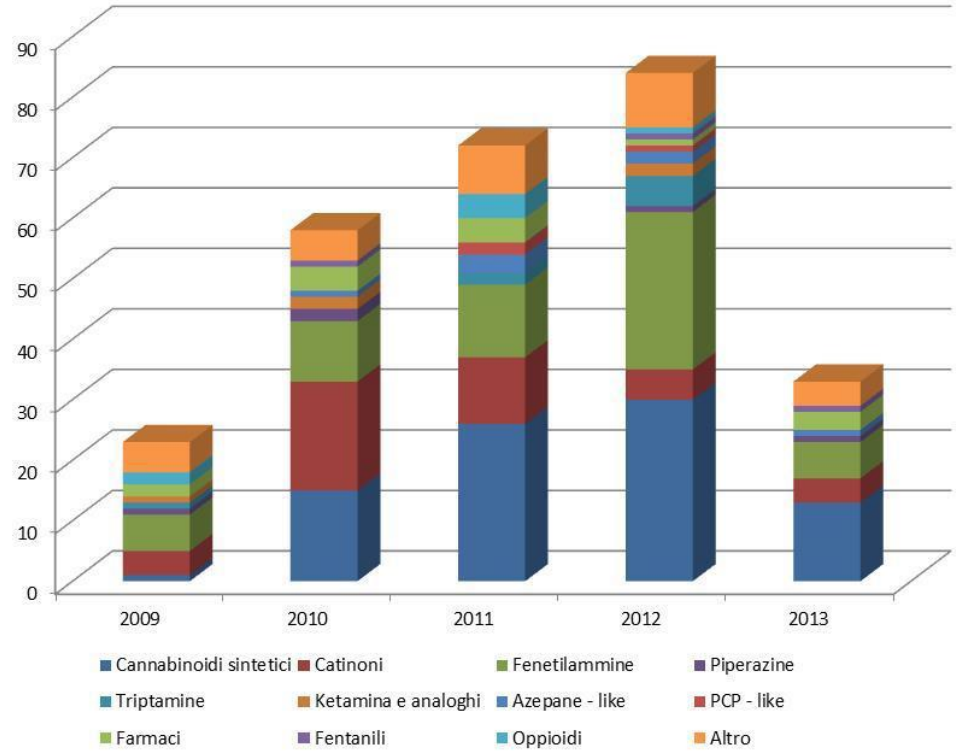



**Figure 4: Italian data on identified NPS (2009-2013) (Source: DPA, 2014).**

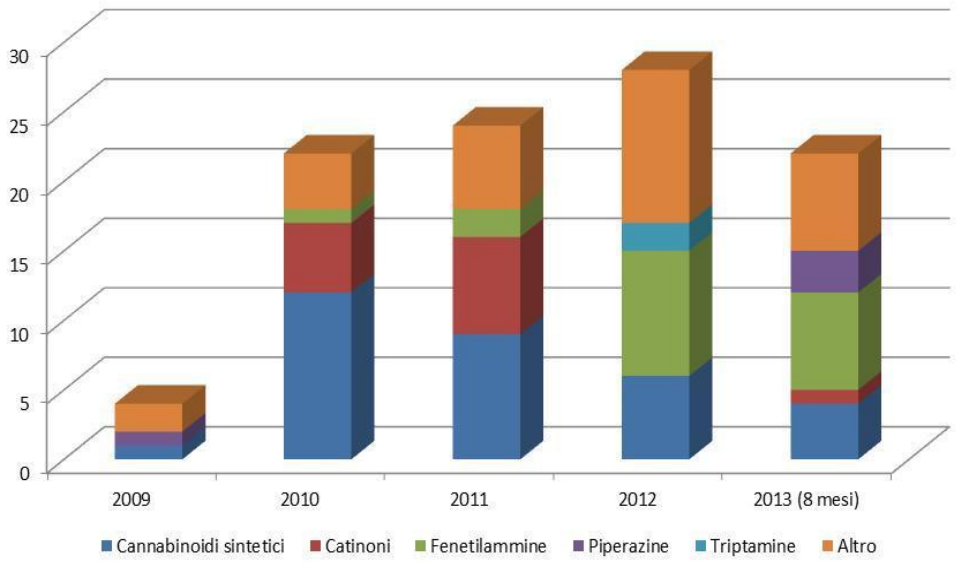



Figure 5: Presence of NPS in Italy (Source: DPA, 2013).

Recently a questionnaire was administrated to 3023 young people aged between 16 and 24 years to investigate the level of knowledge, information and experience with a group of substances (herbal highs, phenethylamines, GHB, synthetic cannabinoids and cathinones). The Italian interviewees declared to know many NPS, especially "bath salts" (26%), *Salvia divinorum* (19.1%), methoxetamine (10.7%) and spices (9%) but also the novel drug called "krokodile" and the class of methamphetamine, while the consumption of NPS seemed limited to synthetic cathinones and cannabinoids. A recent Italian[85] multicentre survey explored the use of NPS in psychiatric populations, detecting a "frequent phenomenon, probably underestimated". The Authors commented these results hypothesising a) the possibility that the use of these compounds is itself a factor able to trigger prodromal symptoms b) subjects with psychiatric disorder may be more motivated to use drugs possibly as self-medicating agents. Another highlighted point in discussion about NPS is that novel compounds may reduce the efficacy of the treatments for psychiatric disorders, worsen symptoms, and reduce the adherence to therapeutic plans.

Table 5: Percentage of use of NPS in Italy amongst general (n=2615) and psychiatric population (n=206) (Source: Martinotti et al., 2014).

| Types of novel psychoactive substances | Percentage use (%) | |
|---|---|---|
| | Healthy subjects | Patients |
| "Spices"<br>Synthetic cannabinoids | 1% | 5.8% |
| "Bath salts"<br>Mephedrone | 0.3% | 0.5% |
| "Ice-shaboo-crystal meth"<br>Methamphetamine | 1.6% | 3.4% |
| Ayahuasca | 0.2% | 0.5% |
| "Nbome-fly-solaris"<br>Phenethylamines | 0.6% | 0.5% |
| Salvia divinorum | 1.1% | 1% |
| Kratom | 0.1% | 0% |
| "Ghb"<br>Gamma hydroxybutyric acid | 0.3% | 1.9% |
| "Special m"<br>Methoxetamine | 0.2% | 1% |

| | | | |
|---|---|---|---|
| "Krokodil" Desomorphine | 0.2% | 0% | |
| **NPS** | **3%** | **9.8%** | P<0.001 |

### *NPS and their unascertained effects*

Drug abuse can have enormous physical, mental and social costs. The NPS phenomenon could represent an increasing risk for public health, especially because their unknown effects. More specifically the use of NPS may lead to erratic symptoms, far beyond the desired recreational effects, and in many cases health services face with multi-intoxication scenario, especially but not limited to emergency services[86,87]. Even if each class of compounds seems to share common chemical structures, the "designed" differences could produce unpredictable results[57] hence the use of NPS, alone or with other substances, can result in acute toxicity with risk of serious harm; in addition there is a paucity of information on NPS pharmacology[9], making it hard to foresee dangers resulting from consumption.

Despite the fact that their origins are not always completely unknown as described above, these drugs of abuse are scientifically relatively new, and need to be examined to determine their a) abuse liability b) level of toxicity and c) their pharmacology as some may be of interest as potential therapeutics. For those reasons attempts to summarize their pharmacological properties must be treated with extreme caution because each individual compound has a distinct "profile"; here-hence the need of specific fact-sheet and/or Technical Folders for every NPS, as for example developed by international agencies and projects (e.g. the ReDNet project). An important limit in this approach is that in many cases when a new product appears in the market there is not enough information, starting from the real composition of the content.

The following description of NPS presented here (Table 6) is based on the identification of six main groups of substances present worldwide in online market according with UNODC[57]: synthetic cannabinoids, synthetic cathinones, tryptamines, phenethylamines, piperazines, plant-based substances, ketamine –like compounds and a seventh group of miscellaneous substances which do not fit into the aforementioned groups, including prescription medicine.

**Table 6: Brief description of main groups of NPS[28,88].**

| | |
|---|---|
| ***Synthetic cannabinoids*** | Cannabimimetics are considered more potent than the THC contained in the natural cannabis plant[29,89]. Negative side effects are several: from cardiac (tachycardia, myocardial ischemia), gastrointestinal (vomiting), neurogical (agitation, confusion), psychiatric (severe hallucinations, and psychiatric disorders called "*Spiceophrenia*"[30]). |
| ***Synthetic cathinones*** | Stimulants, similar to phenethylamines and amphetamines[28,88]. Negative side effects: cardiac (tachycardia, hypertension) pulmonary (breathing difficulties), gastrointestinal (loss of appetite), neurological (increased sweating, deterioration of memory) psychiatric (hallucinations, delusions, erratic behaviour, anxiety, paranoia and depression[90]). |
| ***Phenethylamines*** | They are stimulants and/or hallucinogens and/or entactogenic drugs[91,92]. Negative effects: increased blood pressure, tachycardia, stroke, myocardial arrest, hallucinations, memory loss, psychosis, paranoia[93,94]. |
| ***Piperazines*** | Piperazine-like compounds (e.g. BZP) have euphoric and stimulant properties[95,96]. Adverse effects: tachycardia, hypertension, nausea, urinary incontinence, hallucinations, confusion, psychosis, renal toxicity, seizures[97]. |
| ***Tryptamines*** | Hallucinogenic compounds similar to psilocybin (*Psilocybe* species)[98]. Adverse effects: confusion, dissociative fugue, panic attack[99,100]. |
| ***Ketamine and PCP - like compounds*** | Designer drugs similar to the anesthetic ketamine and |

| | |
|---|---|
| | phencyclidine (PCP)[24,25]; they share dissociative and sedative properties. Adverse effect: fear, anxiety, hallucinations, dissociation and depersonalization[27]. |
| ***Plant –based NPS*** | · Khat (*Catha edulis*) stimulant plant[64,65] originally from East Africa and Arabian peninsula, with risk of psychosis[101].<br>· Salvia divinorum: a popular hallucinogenic a dissociative plant historically used for divination [102].<br>· Kratom (*Mitragyna speciosa*): a tropical plant stimulant at low doses and a sedative at high doses[103], recently used as self treatment of opioid withdrawal[104] .<br>· Ayahuasca: a decoction compound[105] with mild anxiolytics properties[106] and with serious problems of toxicity when associated with serotonergic substances.<br>· *Sceletium tortuosum* ("kanna"): an antidepressant plant from Southern Africa[107,108] .<br>· *Piper methysticum* ("Kava Kava"): an herbal ceremonial drink with anxiolytic properties used as cognitive enhancer [109].<br>· Ibogaine: a psychoactive indole alkaloids from *Tabernate iboga* with terapeutical use for withdrawal but severe side effects [110-112].<br>· *Datura stramonium*: a wild growing plant with ethno-medical potential but severe hallucinogenic risk[113,114]. |
| ***Prescription medicines*** | · Phenazepam: a potent long-acting benzodiazepine [115-117].<br>· Pregabalin: an anticonvulsant drug, approved for neuropathic pain but with a potential for abuse [52,53,118].<br>· Benzydamine: a drug for external use with hallucinogenic properties when ingested[119-121].<br>· Tropicamide: an anti-muscarinic drug that can be abused intravenous [122,123]. |

Given the almost infinite possibilities of altering chemical structures of NPS, there is likewise an infinite number of substances which may differ in effects. For example the phenethylamine class includes well-known stimulant drugs (e.g. amphetamine) but recent NPS (like Bromo-dragonfly or 25-NBoMe group) have reported to have as first effect powerful hallucinogenic properties[6,124-126]. As the same way the heterogeneous group of the synthetic cannabinoids seemed to develop severe dissociative effects inducing psychotic symptoms, far beyond cannabis[29,127-130]. Hence it seems important, especially from a clinical point of view, to describe a) each group of compounds, underlining their main effects but also b) the peculiar profile of each NPS, as in Technical Folders and c) their clinical impact, as for example illustrated in study cases (Phase 3). The list of substances mentioned in each of the NPS groups is not exhaustive but offers some guidance in order to describe the main families of NPS.

*Synthetic cannabinoids*

The appearance of so-called "herbal highs" in the market is not a new phenomenon: such products usually consisted of plant products with little psychoactive effects. Since 2004, however, the composition of these herbal mixtures seems to have substantially changed to include potent new psychoactive compounds known as synthetic cannabinoids[131,132]. Research on the mechanism of cannabis activity dates back several decades when molecules with similar behavior to $\Delta 9$-tetrahydrocannabinol (THC) were first examined. The first synthetic analogue of THC[133] , HU-210, was first synthesized in Israel in 1984 and is considered to have a potency of at least 100 times higher than THC (Figure 6).

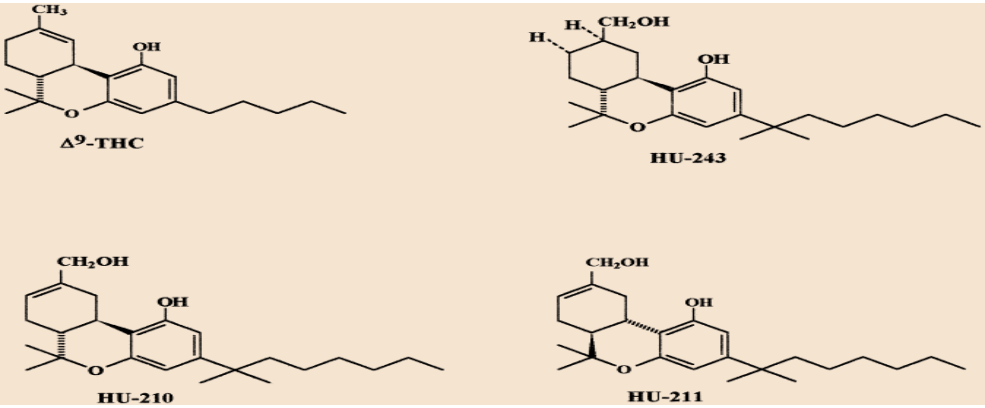


Figure 6: Structures of plant and "classic" synthetic cannabinoids (Source: Mechoulam, 1998).

Due to its similar chemical structure to THC, HU-210 is regarded as a "classical cannabinoid" and has been found in synthetic cannabinoids sold in the United States and other countries[55]. On the other hand non-classical cannabinoids include cyclohexylphenols or 3-arylcyclohexanols (so called "CP compounds") which were developed as potential analgesics by a pharmaceutical company in the 1980s[134]. Respondents to the UNODC questionnaire on NPS have reported the emergence of CP-47,497 and CP-47,497-C8 in numerous countries since 2009. Other structurally dissimilar varieties of synthetic cannabinoids unrelated to THC have also emerged on the market: these include aminoalkylindoles, such as naphtoylindoles (e.g. JWH-018), phenylacetylindoles (e.g. JWH-250), and benzoylindoles (e.g. AM-2233)[134].

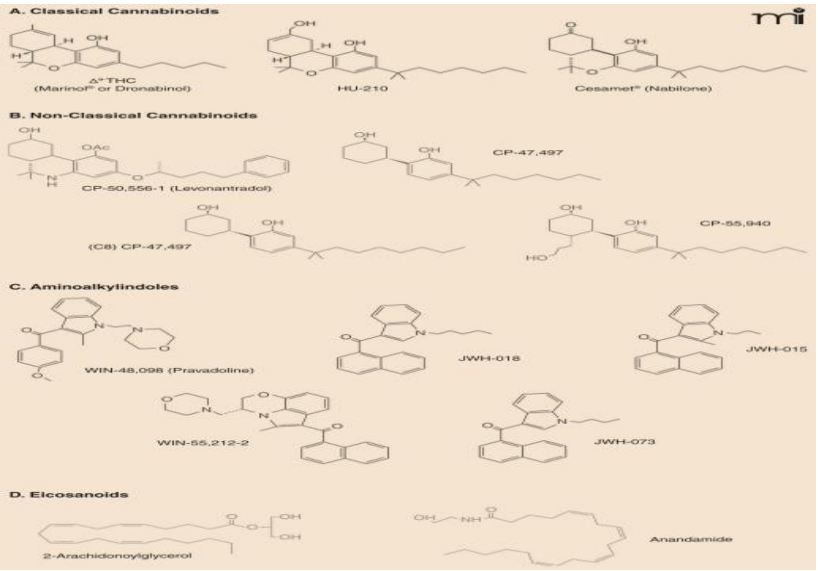


Figure 7: Structural classes of cannabinoid ligands (Source: Seely et al., 2011)

The JWH-compounds had been previously developed by Professor John William Huffman in the United States as test compounds in the research of receptor-drug interactions: these compounds in fact show differential selectivity toward CB1Rs and CB2Rs, the main receptors for THC; for example, JWH-018 and JWH-073 bind both with differing affinities, whereas JWH-015 appears to bind only CB2Rs with high affinity. JWH-018 is arguably the best known synthetic cannabinoid, belonging to the group of aminoalkylindoles and it's considered to be three times as potent as THC[14].

Recent studies and clinical evidences suggest also a high risk from the psychopathologic point of view, in particular an association between synthetic cannabimimetics and psychotic symptoms both in acute and chronic users[30,127]. In addition, a recent ACMD report described in detail the 'third

generation' of synthetic cannabinoids entered in the NPS market in 2013, analyzing chemical core and secondary structures of these compounds[135].

*Synthetic cathinones*

Cathinone (naturally occurring in the leaves of *Catha edulis* plant) and its synthetic derivatives are closely related to the phenethylamine family (which includes amphetamine and methamphetamine), but with a lower potency than the latter[90,136]. They are chemically characterized by the presence of a *β*-keto group on the side chain of the phenethylamines but they share a structural similarity to dopamine, methamphetamine, MDMA, and pyrovalerone[137]. Hence cathinone, the principal active ingredient of the khat plant, is considered as the prototype of this group, causing amphetamine-like and sympathomimetic effects, including tachycardia and hyper-tension as well as psychoactive effects like euphoria and increased alertness. From this substance a range of synthetic cathinones has been developed, since the late 1920s, but NPS synthetic cathinones appeared in online drug markets in the mid 2000s.

Chronologically in 2005, methylone, an analogue of MDMA, was the first synthetic cathinone reported to the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA) while two years after, in 2007, reports of 4-methylmethcathinone (mephedrone) use emerged, first in Israel and then in other countries and regions (including Australia, Scandinavia, Ireland and the United Kingdom)[2,58,138].

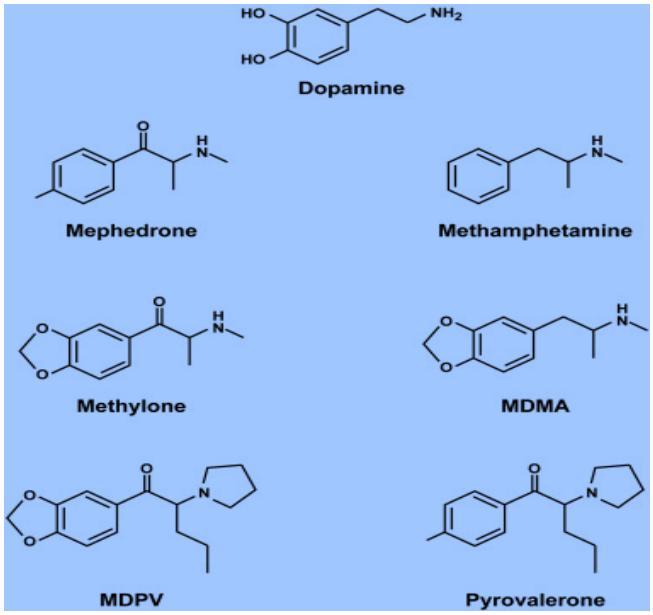



**Figure 8: Chemical structure of dopamine and synthetic cathinones (Source: German et al., 2014).**

Mephedrone (4-methylmethcathinone) was reportedly first synthesized in 1929. Typically, synthetic cathinones have an amphetamine-type analogue effect, however little is known about the mechanism of action and the potential harms of mephedrone, but it has been suggested that mephedrone is likely to act in a similar way to other stimulants (e.g. cocaine, amphetamine and MDMA), rapidly increasing levels of dopamine and serotonin[139]. Up to 2010, methylone and mephedrone were identified as the most common substances of use in this group in Europe[59,60,140-142]. Other synthetic cathinones recently identified in the drug market are also analogues of pyrovalerone (3,4-methylenedioxypyrovalerone and naphyrone).

Another important compound of this group is 3,4-methylenedioxypyrovalerone (MDPV) which was first synthesized in 1969, emerged in 2007 as an NPS in Germany. In 2008, it was first reported to the European Early Warning System by the United Kingdom and by Finland, after being associated with adverse health effects. Initially unregulated, many countries, including members of the

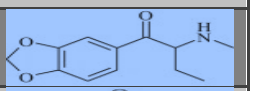
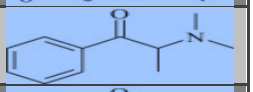
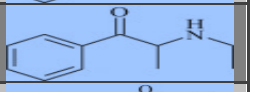
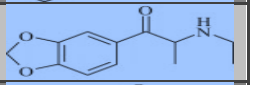
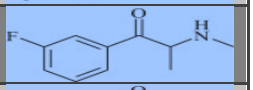
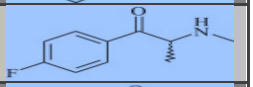
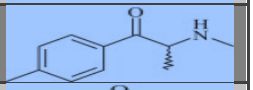
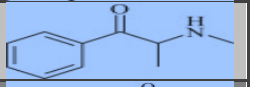
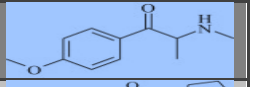
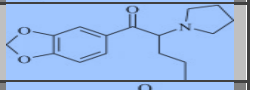
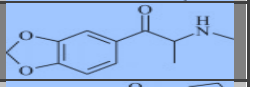
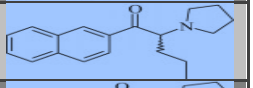
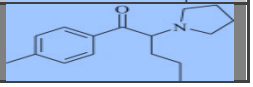
European Union as well as Australia, Israel and the United States have introduced control measures over the substance[143].

Internationally, according to information collected by UNODC[7,57], other synthetic cathinones have increasingly been used as NPS from 2010 onwards, including methylone, butylone, 4-methylethcathinone, 4-fluoromethcathinone, naphyrone, 3-fluoromethcathinone, methedrone, and, to a lesser extent, 3,4-dimethyl- methcathinone, *α*-pyrrolidinopentiophenone (a-PVP), buphedrone, pentedrone and *α*-pyrrolidinopropiophenone (a-PPP).

The medical use of these compounds as therapeutic agents seems limited to bupropion[136], which is structurally a synthetic cathinones with a possible therapeutic role in the treatment of addictive disorders related to these compounds. However recent evidence suggested a recreational misuse also of bupropion[144,145]. Some other synthetic cathinones are pharmaceutical substances such as methylone (patented as an antidepressant and antiparkinsonian agent), diethylcathinone (a.k.a. amfepramone, used as an appetite suppressant), pyrovalerone (marketed for use as an appetite suppressant and in the treatment of chronic fatigue). In some cases these compounds were later withdrawn due to abuse and dependency in users.

A recent review on this group of designer recreational drugs (in general known also as “bath salts”) described current information on their structures and chemical names[140]:

**Table 7 Names and chemical structures of synthetic cathinones (Source: Zawilska et al., 2013).**

| Common name and abbreviation | Chemical name | Chemical structure |
|---|---|---|
| **Butylone (βk-MBDB)** | 1-(1,3-Benzodioxol-5-yl)-2-(methylamino)butan-1-one |  |
| ***N,N*-Dimethylcathinone (methamfepramone)** | (*RS*)-2-dimethyloamino-1-phenylpropan-1-one |  |
| ***N*-Ethylcathinone (EC)** | (*RS*)-2-(ethyloamino)-1-phenyl-propan-1-one |  |
| **Ethylone (4β-MDEA)** | (*RS*)-1-(1,3-benzodioxol-5-yl)-2-(ethyloamino)propan-1-one |  |
| **3-Fluoromethcathinone (3-FMC)** | (*RS*)-1-(3-fluorophenyl)-2-(methylamino)propan-1-one |  |
| **4-Fluoromethcathinone (4-FMC)** | (*RS*)-1-(4-fluorophenyl)-2-(methylamino)propan-1-one |  |
| **Mephedrone (4-methylmethcathinone; 4-MMC)** | (*RS*)-2-methyloamino-1-(4-methylphenyl)propan-1-one |  |
| **Methcathinone (ephedrone)** | α-(Methyloamino)-1-phenyl-propan-1-one |  |
| **Methedrone (4-methoxymethcathinone, βk-PMMA)** | (*RS*)-1-(4-methoxyphenyl)-2-(methyloamino)propan-1-one |  |
| **3,4-Methylenedioxypyrovalerone (MDPV)** | (*RS*)-1-(benzo[*d*][1,3]dioxol-5-yl)-2-(pyrrolidin-1-yl)pentan-1-one |  |
| **Methylone (3,4-methylenedioxy-*N*-methylcathinone; βk-MDMA)** | (±)-2-Methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one |  |
| **Naphyrone (naphylopyrovalerone)** | 1-(Naphthalen-1-yl)-2-(pyrrolidin-1-yl)pentan-1-one |  |
| **Pyrovalerone** | (*RS*)-1-(4-methylphenyl)-2-(pyrrolidin-1-yl)pentan-1-one |  |

*Phenethylamines*

Phenethylamines (or substituted phenethylamines) refer to a class of substances with documented psychoactive and stimulant effects and include a wide variety of drugs (psychotropic compounds, and CNS stimulants, vasoconstrictors [e.g. nasal decongestants], broncho- and vaso-dilators, antidepressants, antiparkinson agents and calcium channel blockers)[146].

In general for what concerns psychoactive compounds, various substituted phenethylamines act mainly as stimulants, and/or as hallucinogenic compounds and sometime as entactogenic substances, affecting the dopamine and serotonin systems of CNS. Specifically in this group are included mescaline (naturally occurring in the peyote cactus, illegal in many countries and prototype of the family), amphetamine, methamphetamine and MDMA, all of which are controlled under the 1971 Convention, and a large group of substances first presented in the book PIHKAL in 1991 and recently available on the online market.

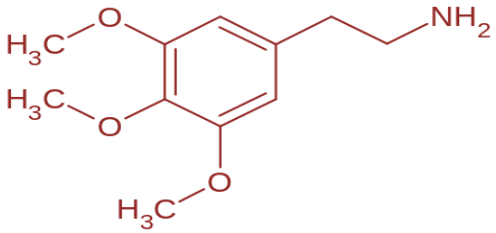
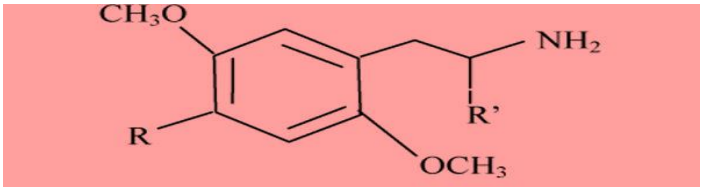



Figure 9: Structure of mescaline.




| | | |
|---|---|---|
| 2C-C | R=Cl | R'=H |
| 2C-D | R=$CH_3$ | R'=H |
| 2C-E | R=$CH_2CH_3$ | R'=H |
| 2C-I | R=I | R'=H |
| 2C-T-2 | R=$SCH_2CH_3$ | R'=H |
| DOC | R=Cl | R'=$CH_3$ |

Figure 10: The synthesis of first substituted phenethylamines.

Synthetically, phenethylamines include a very large number of synthetic drugs belonging to the following main groups, according with their modifications in the chemical structure of mescaline:

- 2C series
- D series
- Benzodifurans
- Other drugs (NBOMe drug series)

To be more precise starting from the 1980s Alexander Shulgin, a biochemist and pharmacologist, reported the synthesis of numerous new psychoactive compounds working on the molecule of mescaline: simple variations on its chemical structures led to the synthesis of powerful new substances (Figure 10). The so called 2C series[92] (classical compounds[147] are: 2C-T-7, 2C-T-2 ) differs from the D series (e.g. DOM[148]; DOC; DOI) only by a slight modification, and their psychoactive effects have been reported to be dose dependent, ranging from mere stimulant effect at lower doses, with hallucinogenic (e.g. 4-bromo-2,5-dimethoxyphenethylamine [2C-B]) and entactogenic effects at higher doses. Years later, in the United States Prof. David Nichols and his research team at

Purdue University synthetized several compounds[149] such as 2C-B, DOB and a range of benzodifuranyl substances (like FLY [tetrahydrobenzodifuranyl] and Dragonfly [benzodifuranyl aminoalkanes]).

**Table 8: Magical Half-Dozen phenethylamines designed by Shulgin.**

| | |
|---|---|
| **Mescaline** | (3,4,5-trimethoxyphenethylamine) |
| **DOM** | (2,5-dimethoxy-4-methylamphetamine) |
| **2C-B** | (2,5-dimethoxy-4-bromophenethylamine) |
| **2C-E** | (2,5-dimethoxy-4-ethylphenethylamine) |
| **2C-T-2** | (2,5-dimethoxy-4-ethylthiophenethylamine) |
| **2C-T-7** | (2,5-dimethoxy-4-propylthiophenethylamine) |

The 2C series, with the addition of methoxy-groups at the 2- and 5-positions, seem to confer hallucinogenic activity: example drugs of this large family are 2,5-dimethoxy-4-bromophenethylamine (2C-B) and 2,5-dimethoxy-4-iodophenethylamine (2C-I). The hallucinogenic properties of these drugs are further enhanced by a methyl-group at the α-carbon (D-Series or hallucinogenic amphetamines). Example drugs included in this group are 2,5-dimethoxy-4-methylamphetamine (DOM), 2,5-dimethoxy-4-bromoamphetamine (DOB), and 2,5-dimethoxy-4-iodoamphetamine (DOI). Chemically benzofurans and benzodifurans belong to ring substituted amphetamines[150]: benzofurans containing one furan ring are for example 6-APB and 5-APB [6-(2-aminopropyl)benzofuran and 5-(2-aminopropyl) benzofuran] and several others. Users report the effects of 5-APB and 6-APB to be comparable to MDMA but more intense[151]. Benzodifurans are a group also known as the "fly" drugs (including Bromo-dragon fly, 2C-B-fly etc.) and are very powerful and dangerous hallucinogen.

Various N-methoxybenzyl-substituted phenethylamines have emerged on the EU drug market since 2012: these drugs such as the NBOMe drug series[152] exert an even higher potency at the 5-HT2A receptor and possibly also at other receptors compared with the already very potent classic hallucinogens. Originally they had been first synthetized in the early 2000s as psychoactive N-methoxybenzyl analogues of the 2C family: the presence of this group ("NBOMe") significantly increases affinities to 5-HT2a receptors and the potency of these substances. The three most available NBOMe drugs online[124-126,153,154] are: 25B-NBOMe, 25C-NBOMe and 25I-NBOMe (see Technical Folder on Phase 3).

Other phenethylamines such as PMMA, first synthesized in 1938, are also sold in the drug market as a substitute for ecstasy, in combination with PMA (a substance listed in Schedule I of the 1971 United Nations Convention on Psychotropic Substances)[155,156].

The new presence on the online market of these compounds is an example of the misleading term "legal highs": they are apparently novel but in many cases already listed in Schedules I and II of the 1971 Convention (2C-B, brolamphetamine (DOB), STP/DOM, MDE, 4-MTA) and they can be sold as illegal ecstasy (for example PMA). At the same time many compounds of the new available substances such as the 2C series, the D-Series and others such as PMMA are not under international control.

*Piperazines*

Piperazines have been described as "failed pharmaceuticals"[95,157], as some had been evaluated as potential therapeutic agents, even if they were never brought to the market. While the best known piperazine that has been used as a new psychoactive substance is 1-benzylpiperazine (BZP), during the last decade other compounds appeared: 1-(3-chlorophenyl) piperazine (*m*CPP), 1-(3-trifluoromethylphenyl) piperazine (TFMPP), 1-Benzyl-4-methylpiperazine (MBZP) and 1-(4-Fluorophenyl)piperazine (*p*FPP) (Figure 11).

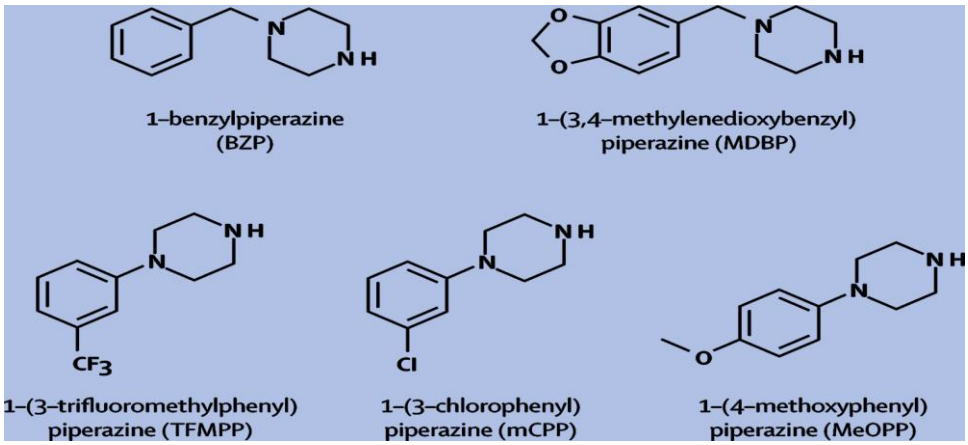


Figure 11: Chemical structure of piperazines.

Basically these compounds are designer drugs that mimic the molecular mechanism of 3,4-methylenedioxymethamfetamine (MDMA)[158], and they act in a similar way inducing a release of serotonin and dopamine, even if at different levels[159] . Their history began as drugs in medical research field: piperazinic compounds were used as anti-helmintic agents around 1950s, BZP for example was investigated and abandoned as antidepressant in 1970s while, in 1980s, piberaline was developed as a stimulant in Hungary and Spain but later withdrawn. Their misuse as "party pills" began in the late 1990s, when BZP emerged in New Zealand as a "legal alternative" for MDMA and methamphetamine; few years later this NPS was reported in Europe. The compound is now banned in several countries and it is probably the most studied piperazine [160,161162].
*M*CPP, reportedly more widespread than BZP in some regions, was developed during the late 1970s and is an active metabolite of therapeutic drugs such as trazodone and nefazodone, used as antidepressants and minor tranquilizers. TFMPP is closely related to MCPP, is almost always found in combination with BZP, sold as "ecstasy". Piperazines are not under international control, although several (BZP, TFMPP, *m*CPP, MDBP) were pre-reviewed by the WHO Expert Committee on Drug Dependence in 2012.

*Tryptamines*
Some tryptamines are natural neurotransmitters while most are psychoactive hallucinogens found in plants, fungi and animals as amine alkaloids. Natural tryptamines include serotonin, melatonin, bufotenin, 5-Methoxy-*N*,*N*-dimethyltryptamine (5-MeO-DMT) and dimethyltryptamine (DMT).
Other Tryptamines have been synthesized for pharmaceutical purposes to combat medical conditions (e.g. sumatriptan and zolmitriptan to treat migraine), but they have also been used as NPS.

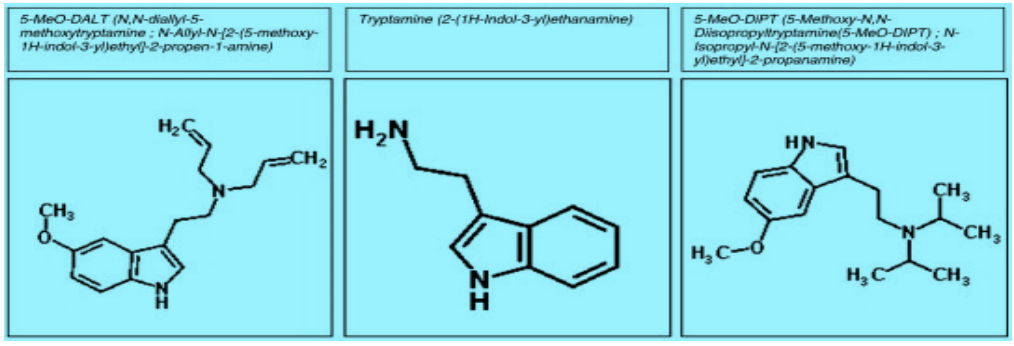


Figure 12: Chemical structures of three new tryptamines.

The prototypes of this family are psilocybin and bufotenin, well known hallucinogenic compounds both naturally available and used for recreational purpose. The misuse of psilocybin (a natural

hallucinogen found in certain species of mushrooms) was popular in the late 1950s in the United States while bufotenin (secretions of the toad *Bufo alvarius*) has also been reported as a street drug. Synthetic modified tryptamines appeared in illicit drug markets only in the 1990s, and recently increased according with UNODC data[57]. For example, the Drug Enforcement Administration of the United States reported that the estimated number of tryptamine reports rose from 42 to 474 in only 4 years (2006-2010). UNODC[7] and EMCDDA[163] describe an abuse of both natural and synthetic tryptamines[87,99,100] including: 5-Meo-DALT, 5-MeODMT, 5-MeO-DPT, AMT, 4-AcO-DMT, 4-AcODiPT, and 5-HTP. It's relevant to notice that psilocin, psilocybin, DET, DMT, and etryptamine are the only tryptamines under international control (listed in Schedule I of the 1971 Convention) while some others are restricted at the national level in several countries.

*Ketamine or PCP –like compounds*

Ketamine is an anesthetic drug with hallucinogenic and dissociative properties (associated hallucinogenic effect is the so called "K-hole" experience); it is closely related to the internationally controlled drug phencyclidine (also known as PCP or "angel dust"), which is listed in Schedule II of the 1971 Convention[164].

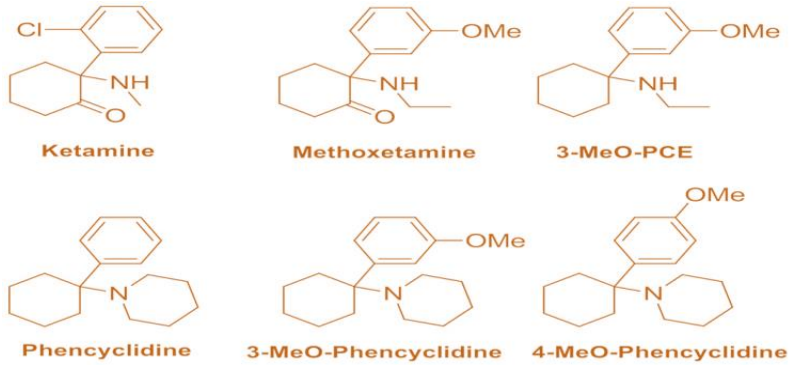



**Figure 13: Chemical structure of ketamine, PCP, methoxetamine and other analogues.**

Phencyclidine was investigated as an intravenous anaesthetic, sold until 1967 as an injectable drug in the United States under the trade names Sernyl and Sernylan in the 1950s but was later withdrawn due to undesired hallucinogenic and delirium effects. Following the withdrawal of phencyclidine, ketamine was synthesized firstly as an anaesthetic in 1962 and marketed few years later as a medical alternative to phencyclidine, used today in veterinary clinic. Despite its use psychoactive substance as a dissociative/hallucinogenic drug and a series of risk assessment through years, a range of international agencies, in particular WHO and European Commission, decided that it would not be appropriate to introduce international control measures.

Ketamine / PCP-type like new designer compounds appeared for the first time in Europe starting from 2010 as "research chemicals"[164]: 3-methoxyeticyclidine (3-MeOPCE) was reported to the European Early Warning System in the United Kingdom (2010), and in 2011 4-methoxyphencyclidine (4-MeO-PCP) was identified in Norway, Russian Federation and the United Kingdom and as the most common PCP-type substance by UNODC. Another substance, called methoxetamine (MXE) [27,165,166] seemed to be particularly common, sharing a similar chemical structure and some properties of ketamine ("M-hole"), but with stronger and longer effects. MXE acts as NMDA antagonist, with an activity also as dopamine releaser and serotonin transporter inhibitor. Other drugs with a similar action, especially at the NMDA receptor, are for example diphenidine (DND), methoxphenidine (MXP), dextromethorphan (DXM)[9].

PCP and phenylcyclohexyl analogues including eticyclidine (PCE), rolicyclidine (PHP, PCPY), tenocyclidine (TCP) are controlled in Schedule I of the 1971 Convention but derivatives such as 3-MeO-PCE and 4-MeO-PCP are not under international control.

*Plant based NPS*

The khat shrub (*Catha edulis*) of the celastraceae family is a plant native to the horn of Africa and the Arabian Peninsula. In these regions khat chewing is a social custom while in Europe and North America khat was considered to be traditionally used by migrant communities, but recent studies and reports[64] highlighted that its use has spread beyond these communities, becoming a popular plant based substance. The stimulant psychoactive effect results from the release of cathinone and cathine alkaloids, two ingredients isolated respectively in 1975 and 1930. *Catha edulis* is not under international drug control, but cathinone and cathine are listed in Schedules I and III. Khat is under national control in several countries.

Kratom *(Mitragyna speciosa* of the *Rubiaceae* family, see Techical Folder in Phase 3) is a large tree found in tropical and sub-tropical regions of South-East Asia. Kratom contains many alkaloids (including mitragynine, mitraphylline, and 7-hydroxymitragynine)[103] and traditionally it had been used in Malaysia and Thailand by workers to enhance productivity, as a substitute to opium[104] in traditional medicine, allegedly due to its morphine-like pharmacological effects. In the early 2000s Kratom[131,167] became available in Europe but with misleading labeled products: first herbal products with *'kratom acetate'* or *'mitragynine acetate'*, do not contained mitragynine, but main ingredients were caffeine and synthetic O-desmethyltramadol ("*krypton")*. More recently, other products have been sold but with differences concerning concentration of the active components (mitragynine and 7-hydroxymitragynine) and at the same time EMCDDA revealed that kratom (2008-2011) can be considered one of the most widely offered NPS. Neither kratom nor any of its active alkaloids are listed under the 1961 and 1971 Conventions, but several countries have adopted control measures.

*Salvia divinorum* (of the mint family Lamiaceae), is a psychoactive plant indigenous to forest areas in Oxaca (Mexico) with a traditional use by the Mazatec Indians for religious practices and medical purposes[168-170]. Its active ingredient is Salvinorin A, a terpenoid responsible for the psychoactive effects of the plant, which incudes visual hallucination and dissociative effects. The chemical mechanism of Salvinorin A is an action as agonist of the k-opiod receptor. Neither *salvia divinorum* nor salvinorin A are under international control, even if literature and reports highlighted this plant as a popular and widespread NPS[40,168,171-174] and many countries banned this herbal product.

*Prescription medicines*

Many prescribed drugs could be enlisted amongst NPS because of a) their abuse liability b) the fact that they be illegal in different areas. Scientific literature and international reports suggest that some medicines in fact can be misused as recreational compounds, even without the doctor's prescription, for example:

- Phenazepam (called also "bonsai", "zinnie") prescribed in Russia for neurological and other disorders and pyrazolam are two powerful benzodiazepines; "zinnie" was involved in recent deaths in Europe due its abuse[115-117].
- Pregabalin is a common prescription drug in Europe for generalized anxiety disorder and other neurological diseases[52,175-177]; several evidences underlined its misuse as a recreational drug due to euphoric and psychedelic effects[53,54,118,178,179].
- Tropicamide is an antimuscarinic drug usually prescribed as an ophthalmic solution to induce short-term mydriasis and cycloplegia but also reported as a self-administrated recreational substance especially in Russia[122,123,180].
- Benzydamine hydrochloride is a non-steroidal anti-inflammatory drug used topically to treat lesions of mucosa; recently this substance was ingested at high dosage with recreational purpose but with severe side effects (hallucinations and agitation) [119,181-183].
- GHB (gamma-hydroxybutyric acid) is a drug used in alcohol withdrawal and narcolepsy, acting as an agonist of GABA –A/B receptors with high additive properties; together with its precursor (GBL, gamma-butyrolactone) GHB is a popular "club drug" (also called "liquid ecstasy") and associated with several fatalities[184-187].
- Baclofen is another GABA-B agonist able to induce anxiolytic effects and relaxation but with the risk of abuse, overdose and lethal consequences[188-190].

· Recent evidence suggested a misuse of common psychiatric treatments self administrated at high dosage (e.g. olanzapine, quetiapine and venlafaxine)[9].

*Others*

Several recent NPS do no belong to previous cited classes and have emerged in last years, for example:

- Synthetic opioids, which can mimic morphine and heroin: AH-7921 [191](called "doxilam") firstly synthetized in 1970s but which was available as NPS since 2012 and responsible of confirmed intoxications in Europe, USA and Japan[192] ; MT-45; nortilidine; W15; W18; 4FBF; IC-26[9].
- Stimulants and cocaine substitutes: 4,4'-dimethylaminorex (4,4'-DMAR) an amphetamine like stimulants derivate from aminorex [193]; methiopropamine (MPA)[194]; RTI-111, RTI-121 and RT-126 which are powerful stimulant chemically analogue of cocaine[195].

***NPS and role of healthcare professionals***

Many of the NPS may be considered unpredictable psychoactive substances in their desired, medical and psychopathological effects. Novel psychoactive drugs acts mostly as stimulants and/or hallucinogens with a severe risk for public health: first of all, their acute toxicity is often a reason for accessing health services, which might not be able to identify erratic symptoms, characterize single substances and choose an appropriate treatment. Therefore errors in the assessment phase, with the risk of mistakes on diagnosis and managements of patients might also occur.

Actually, NPS users seeking help may have contact with different health professionals, such as a) physicians in Departments of Addiction, b) psychiatrists in the Mental Health Services c) General Practitioners but also d) Paediatrics, (especially in consideration of the young age of some of these clients and, of course, e) professionals working Emergency Rooms. However, as a matter of fact, most people using NPS are not coming to the attention of specialist drug treatment services: they are reluctant to get help from services perceived for "classic" drugs (alcohol, heroin, cocaine)[80]. On the other hand health professionals of all services are often not aware of these agents when new NPS become available on the market[196].

Consequently, initial information on a) *names/street names* b) *patterns of toxicity* c) *adverse side effects* are crucial for health professionals in order to explore the expanding galaxy of NPS. Initially these data are collected from the analysis of the discussion on their effects among users on online fora[5,197]; only subsequently single case report may be useful to attribute toxicity, to weigh the clinical impact of a novel compound, hopefully with an analytical confirmation.[26,198-200]

Indeed there's a paucity of reliable information both for health professionals and users: NPS are rarely mentioned in scientific literature and their effects and potential risks are mostly unknown[50,201]. In the last decade the emergence of novel psychoactive drugs has raised prominent issues in the fields of substance use research[202]; in fact, although the phenomenon is well known since 2003[203] and as the case of mephedrone in the UK in 2010 dramatically suggested[59,138,204-206], appears to be essential to provide up-to-date and reliable sources of information to health professionals[207,208] .

This may be a reason for concern particularly for the emergency departments, where both general physicians and psychiatrists may not be able to carry out a proper medical assessment due to the limited knowledge of NPS. In the context of classic substance abuse in general, it is well-known that an accurate diagnosis could be difficult due to limited historical information available and the fact that clinicians neglect to ask about substances[209]. For example an interesting study of the Department of Psychiatry at the Columbia University highlighted that in emergency departments a high percentage of patients (almost a quarter) diagnosed as primary psychotic disorders had substance-induced psychosis or even no psychosis. Authors underlined that a such misdiagnosis should be a concern because of diagnostic error as well as the long- term treatment implications for

the patient, the associated stigma, the tendency for the diagnosis to be perpetuated in further encounters with psychiatrists, the inappropriate use of antipsychotic medications and hospitalizations, the concrete risk of no follow-up substance abuse treatment, and in general negative outcomes (rehospitalisations, substances abuse etc.). The study was conducted in 2006, including alcohol, cocaine, cannabis substance use disorders, without considering the most recent "epiphany" of synthetic cathinones and cannabimimetics[210], whose evidences reported severe risks of psychotic breakdown and psychiatric symptoms as acute consequences: it is not only a speculation here that the clinical impact of NPS is going to increase these errors in the assessment phase with severe repercussions on the patient's life.

In order to truly understand what could be the actual magnitude of the phenomenon, a recent study conducted in Sweden by the Karolinska University, called STRIDA project, confirmed the widespread presence of NPS in emergency departments (Table 9)[87]: authors here detected a large presence of novel compounds and classic substances, with concerns for a multi-substances intoxication scenario, where classic compounds (e.g. alcohol and cannabis) are consumed with novel substances in almost 40% of cases[86,87].

**Table 9: Substances identified among 189 consecutive cases submitted from January 2010 to August 2011 for toxicological analysis within the STRIDA project on new psychoactive substance (NPS) use in Sweden. (Source: Helander et al., 2014, modified).**

| Sub-grouping of substances | Substances (alternative/trade names) | Positive samples ,*N* (%) | Single substance intoxications |
|---|---|---|---|
| **Natural** | Cannabis | 37 (19.6%) | 7 |
| **Synthetic** | JWH-015 | 4 (2.1%) | 2 |
| | JWH-018 | 4 (2.1%) | 4 |
| | JWH-019 | 3 (1.6%) | |
| | JWH-081 | 13 (6.9%) | 7 |
| | JWH-210 | 6 (3.2%) | 4 |
| | JWH-250 | 2 (1.1%) | |
| **Phenylpiperazines** | para-Fluorophenylpiperazine (pFPP) | 1 (0.5%) | |
| | 3-Trifluoromethylphenylpiperazine (TFMPP) | 1 (0.5%) | |
| **α-Methylated phenethylamines** | Amphetamine/methamphetamine | 17 (9.0%) | 5 |
| **Ring-substituted amphetamines** | 4-Fluoramphetamine (4-FA, 4-FMP) | 3 (1.6%) | |
| | 4-Methylamphetamine (4-MA) | 5 (2.6%) | |
| | Paramethoxyamphetamine/paramethoxymeth amphetamine (PMA/PMMA) | 3 (1.6%) | |
| **β-Ketonated amphetamines**[e] | 3,4-Dimethylmethcathinone (3,4-DMMC) | 2 (1.1%) | |
| | 3-Fluoromethcathinone (3-FMC) | 1 (0.5%) | |
| | 4-Fluoromethcathinone (flephedrone, 4-FMC) | 1 (0.5%) | |
| | Methcathinone (ephedrone) | 2 (1.1%) | 1 |
| | 4-Methoxymethcathinone (methedrone) | 2 (1.1%) | |
| | α-Methylamino-butyrophenone (buphedrone) | 3 (1.6%) | |
| | α-Methylamino-valerophenone (pentedrone) | 1 (0.5%) | |
| | 4-Methylethcathinone (4-MEC) | 7 (3.7%) | 1 |
| | 4-Methylmethcathinone (mephedrone, 4-MMC) | 6 (3.2%) | |
| | 4′-Methyl-α-pyrrolidinopropiophenone (MPPP) | 2 (1.1%) | |
| | Naphtylpyrovalerone (Naphyrone) | 2 (1.1%) | |
| | α-Pyrrolidinopentiophenone (α-PVP) | 3 (1.6%) | |
| **Methylenedioxyphenethylamines** | | | |
| **Ring-substituted methylenedioxyphenethylamines**[e] | Butylone (bk-MBDB) | 4 (2.1%) | 1 |
| | 3,4-Methylenedioxypyrovalerone (MDPV) | 10 (5.3%) | 2 |
| | Methylone (bk-MDMA) | 6 (3.2%) | 1 |
| | Pentylone (bk-MBDP) | 1 (0.5%) | |
| **Natural** | Psilocin | 3 (1.6%) | 3 |
| **Synthetic** | 4-Hydroxy-*N*-methyl-*N*-ethyltryptamine (4-HO- | 14 (7.4%) | 11 |

| | | | |
|---|---|---|---|
| | MET) | | |
| **Piperidines** | Desoxypipradrol (2-DPMP) | 8 (4.2%) | 4 |
| **Plant related** | Mitragynine, with or without *O*-desmethyltramadol | 5 (2.6%) | 1 |
| **Pharmaceutical related** | Buprenorphine | 2 (1.1%) | |
| | Dextromethorphan (DXM) | 2 (1.1%) | 1 |
| | Ethyl morphine | 1 (0.5%) | |
| | Fentanyl | 1 (0.5%) | 1 |
| | Methadone | 3 (1.6%) | |
| | Morphine alkaloids | 10 (5.3%) | 1[f] |
| | Norpropoxyphene | 1 (0.5%) | |
| | Pethidine | 1 (0.5%) | |
| | Tramadol/*O*-desmethyltramadol | 12 (6.3%) | 1 |
| **Ketamine and related substances** | Ketamine | 2 (1.1%) | |
| | Methoxetamine (MXE) | 3 (1.6%) | |
| **GABA analogues** | Gamma-hydroxybutyric acid (GHB) | 1 (0.5%) | |
| | Pregabalin | 12 (6.3%) | 1 |
| **Other classical abusing agents** | Benzodiazepines, common | 40 (21.2%) | 6 |
| | Benzodiazepines, phenazepam | 3 (1.6%) | 3 |
| | Cocaine | 2 (1.1%) | |
| | Dimethocaine | 2 (1.1%) | |
| | Ethanol and/or ethyl glucuronide (EtG) | 57 (30.2%) | 18 |
| | Pentobarbital | 4 (2.1%) | 2 |
| **Drug negative samples** | – | 33 (17.5%) | |

So the key points presented here are a) the presence of the ever-changing galaxy of NPS in emergency departments b) the difficulty of recognising their psychiatric symptoms in ER services c) the resulting risks for NPS patient in term of appropriate assessment and adequate treatment.

Apart from the acute access to urgent care unit, NPS users[211] seem not to consult specialist drug treatment services, perceiving these services "unfitting" for their needs: these services indeed are probably more familiar with alcohol, opiate and crack cocaine related harms. As a matter of fact, patients may have to contact mental health services (exhibiting consequences of NPS, such psychomotor agitation, depression or psychotic symptoms), to primary care services and General Practitioners (complaining organic symptoms) or to paediatrics services (considering diffusion of NPS amongst young people), but also to sexual health services (NPS in fact can be used by LGBT communities to enhance sexual performances). An important observation, derived by online fora, scientific literature, national and international reports, is that the NPS users are not classic drug abusers: they seem to be a different population, including students researching a recreational "legal high"[40,142,173], clubbers and ravers who use NPS in different dance contexts[22,212-214], psychiatric patients trying to self-medicate[85], psychonauts able to access to online secret marketplaces such as Silkroad[215-217], professionals (and students) who search to improve their performance and cognitive skills[34,38], online clients surfing internet searching remedies to their sexual and appearance issues[37,218-220], Lesbian-Gay-Bisexual-Transgender (LGBT) communities trying to improve their sexual life[221,222].

These features, concerning the problematic use of NPS, different populations of users and unascertained effects in their misuse, require healthcare professionals to develop specific interventions in order to avoid inappropriate or even dangerous treatments, including detoxification for in-patients and outpatients, psychological and psychosocial treatments, referral and support for health issues, etc. As well described by a Royal College of Psychiatrists document[80] addiction services (in the UK) are unprepared, with a "handful of specialists and dedicated services" for this new problem, even if with a steady demand for treatment by these novel users. The report started from data of the National Drug Treatment Monitoring Service (2013) showing how the number of presentations requiring a treatment for NPS increased and highlighting how current services are not able to answer to these patients. The Author suggests to a) change traditional services attitude towards novel compounds b) support both drug and no-drug service staff educating about NPS c)

exchange information, knowledge and expertise about new compounds d) record presence, diffusion and harm risks of NPS in all departments with a monitoring system e) promote researches also for the treatments f) expanding awareness in general public with reliable information.

## The need of rapid and innovative forms of prevention: the role of the Recreational Drugs European Network (ReDNet) as a successful model

*The ReDNet project*

One of the first attempts to develop effective prevention models targeted at NPS phenomenon was carried by the Recreational Drugs European Network (ReDNet) a research project led by the University of Hertfordshire. ReDNet aimed at studying novel psychoactive drugs, improving the level of information on NPS and exploring innovative communication technologies. ReDNet was able to disseminate results to professionals, producing scientific literature, specific technical folders on NPS but also use multimedia tools, social networking and mobile phone technology[5,197,223]

The ReDNet project was funded by the European Union (Health Programme, grant number: A/800102; 2006 348) and represents an example of a successful multi-site implementation project developed by the University of Hertfordshire (UK) in partnership with ten research Centers across eight EU countries (Table 10).

**Table 10: Partners of the ReDNet project.**

| |
|---|
| · **University of Hertfordshire** |
| · **National Addiction Centre, Institute of Psychiatry, King's College London, London, UK** |
| · **Institute of Psychiatry and Neurology, Warsaw, Poland** |
| · **Bergen Clinics Foundation, Bergen, Norway** |
| · **De Sleutel, Gent, Belgium** |
| · **Servizio Salute Regione Marche, Ancona, Italy** |
| · **Consorci Mar Parc de Salut de Barcelona, Spain** |
| · **Rhine State Hospital, University of Duisberg-Essen, Essen, Germany** |
| · **National Institute for Drug Prevention, Institute for Social Policy and Labour, Budapest, Hungary** |
| · **DrugScope, London, UK** |

ReDNet was also supported by the UNESCO Chair in Information and Computer Ethics, for its emphasis on prevention services based on technological tools (ICT). In addition, during its activity the research team collaborated with national and international networks of collaborators including many agencies and departments as outlined in Table 11.

**Table 11: Selected list of collaborating partners of the ReDNet project.**

| |
|---|
| · **United Nations Office on Drugs and Crime (UNODC), Vienna, Austria** |
| · **Eotvos Lorand University, Budapest, Hungary** |
| · **National Antidrug Agency, Rome, Italy** |
| · **National Antidrug Agency, Bucarest, Romania** |
| · **Addictologie, Prague, Czech Republic** |
| · **Children's Society, London, UK** |
| · **ELISAD, London, UK** |
| · **State Psychiatric Hospital of Alcohol and Drug Addiction, Sofia, Bulgaria** |
| · **Trimbos Institute, Utrecht, Netherlands** |
| · **A-Clinic Foundation, Helsinki, Finland** |
| · **Institute for Research and Development "Utrip", Grosuplje, Slovenia** |
| · **University of Szczecin, Poland** |
| · **La Sapienza - Università di Roma, Italy** |

- **Università degli Studi G. D'Annunzio, Chieti-Pescara, Dipartimento di Neuroscienze, Italy**
- **Dipartimento Dipendenze Patologiche di Macerata, Italy**
- **Università degli Studi di Padova, Dipartimento di Psichiatria, Italy**
- **Casa di Cura Parco dei Tigli, Padova, Italy**

The ReDNet project started in April 2010 and ended in June 2012, and aimed to develop: a) *accurate information on new recreational drugs* b) *innovative and effective ICTs to disseminate this information (e.g. mobile technology, social networking, virtual learning environment);* c) *new strategies of prevention, harm reduction and research in the NPS field*.

The use of ICT tools has been an essential point to reach ReDNet main objectives. As discussed the diffusion of NPS has been facilitated by online markets and Internet accessibility: as a matter of fact most people currently obtain information about NPS from online websites, where drug using experiences are shared and clients can easily buy these compounds in the cyber market, including Silk Road[163,216] and obtain medical products on online pharmacies without prescription[219,220]. The main point here is that information on new designed compounds is described firstly in online fora, and only in a second time scientific literature is able to describe and characterize single NPS (e.g. the cases of mephedrone [59] and methoxetamine [24,27]).
For this reason the ReDNet project has emphasized the importance of drug prevention activities and the dissemination of information among health professionals especially using ICT tools, which can provide rapidly reliable data from a reliable source. The project for example designed an online interactive website (www.rednetproject.eu), SMS alerts systems, social networking (a Facebook page and a Twitter account), multimedia resources (a channel on You Tube), smartphone applications (iPhone) and virtual learning environments (Second Life) to promote the rapid diffusion of evidence-based information amongst vulnerable individuals and professionals internationally. After the end of ReDNet (May 2012), a pilot integrated and free SMS-Email system, called SMAIL (SMS and EMAIL information Service; later rebranded as HighWise) has been further developed and promoted. The SMAIL Service was specifically designed for health professionals, who can receive automatically a message (SMS and Email) with descriptive key points for texted compounds (see Methods and Phase 2).
Overall, the ReDNet project was very successful and has been cited by the Advisory Council of Misuse of Drugs as an effective European initiative in order to build knowledge and evidence-based practice in harm reduction[1]. The ReDNet project was also awarded in the 2013 European Health Award for its outstanding contribution in the field of public health: it was judged as a prolific initiative "involving collaborative working", "which contributes in a clear and significant way to meeting some of the challenges facing Europe".
Last but not least, the research team has produced over 50 peer reviewed scientific articles, 150 presentations at conferences and seminars, and also contributed to the public debate through mass media channels with general articles, press releases, TV and radio interviews.

## AIM AND RESEARCH QUESTIONS

Within the broader scope of ReDNet, the core aim of this research project was to understand and explore health professionals' knowledge and awareness on NPS, while informing and contributing to the development of rapid and appropriate channels of dissemination. In fact the very definition of the phenomenon seems to be recent and maybe unfamiliar for healthcare professionals; specifically this research work aims to evaluate and expand the expertise of health professionals on NPS.

The key objectives are (Figure 14):

1) To assess the level of knowledge and awareness on NPS amongst a sample of Italian health professionals, exploring in particular their preferred channels/media/electronic tools to gather up-to-date information relating to NPS.

2) To evaluate the effectiveness of the dissemination tools developed by The Recreational Drugs European Network (ReDNet), collecting feedback from the international network of health professionals attached to the project and in particular exploring the first automated SMS –Email service (SMAIL) developed by the team.

3) To understand the clinical impact of NPS through specific and up-to-date technical folders, exemplifying the study of novel substances (Alpha-PVP, Kratom, 25I-NBOME and Bromo-dragonfly) and through two clinical case reports collected in the field ("*Alice in wonderland*" and "*Paranoid android: Marvin*").

The final outcome of this project is to provide recommendations on the future development of appropriate dissemination/guideline tools designed for professionals, with the aim of filling the existing gap between NPS and European health professionals, while helping them "not to be lost" in the expanding NPS galaxy.

Table 12: Main research questions of this project

| |
|---|
| **What is the level of awareness and expertise on NPS amongst health professionals?** |
| **What is the level of awareness of NPS intake associated risk?** |
| **What is the professionals' clinical experience about treatment and management of NPS intake?** |
| **What are HPs' preferred channels or tools to receive information relating NPS?** |
| **What is the impact of a project like ReDNet as a prevention model?** |
| **What are the preferred channels of information developed during the ReDNet project?** |
| **Could the SMAIL be a useful service to expand expertise on NPS?** |
| **Could the SMAIL service promote a reliable and up-to-date circle of information through its facts-sheets?** |
| **How can be structured a synthetic technical folder to help health professionals?** |
| **How could be exemplified the clinical impact of NPS?** |
| **Could be useful the analysis of clinical case reports to better understand the galaxy of NPS?** |
| **How health professionals could be guided in this "expanding galaxy"?** |

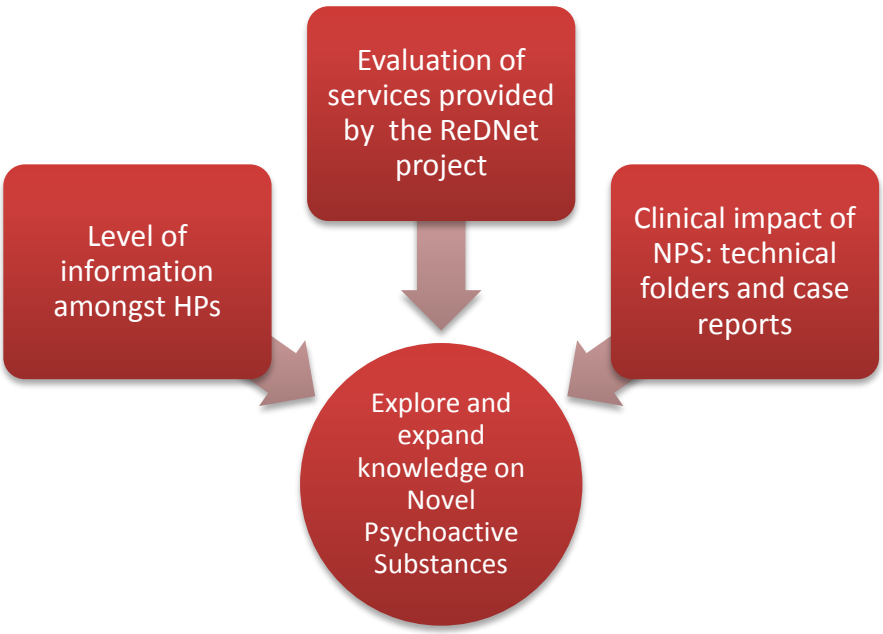



**Figure 14: Three main phases developed during the research project.**

## METHODOLOGY

According to the core objectives, the methodological approach has been articulated in three main phases. *Phase 1* assessed knowledge of NPS in a sample of Italian health professionals using a specific online questionnaire[224], with the aim to understand and highlight what could be the preferred channels of information; *phase 2* evaluated services provided by ReDNet[5,197] project through an international survey available to subscribed health professionals; in the same phase was evaluated the pilot SMAIL service; *phase 3* described how gathered information on NPS[24,123,125], in form of Technical Folders, can be an useful tool for health professionals in everyday work, exemplified by two case reports of firstly recognised users of NPS encountered in my activity as psychiatrist.

### Phase 1: Investigating the level of knowledge and preferred channels of information for health professionals in Italy.

*NPS survey among Italian health professionals*

The ReDNet NPS survey was originally conceived to be available in a range of different languages in order to allow carrying out proper interviews with health professionals across the eight partner countries (United Kingdom, Italy, Germany, Spain, Belgium, Poland, Hungary and Norway).
The original questionnaire was designed in English and investigated novel substances reported by EMCDDA and also collected on the ReDNet database. The main aim of the project was to assess the awareness on NPS amongst health professionals across Member States.

Specifically, I was in charge of the Italian study. I prepared the Italian version of the questionnaire, by adding original sections on NPS psychopathological concerns amongst professionals; with this additional section (see Table 13) my attempt was to gain a better understand what the clinical consequences of novel recreational compounds are in the field, directly questioning physicians for their opinion. I prepared a study protocol and applied for ethics approval (see below) at the Ethics Committee of the University of Padova. I also made contact with Clinical Directors of each services operating in the North-East of Italy to explain and promote the questionnaire. Therefore, I personally recruited healthcare professionals distributing e-mail with the link to the survey (or the paper version if requested). I also liaised with DPA for further support at the national level. Finally, I carried out the analysis of the results using SPSS and contributed as a main author to the publication of the study [224].

The version presented here (Appendix 2) was based on the Italian translation of the EU-wide questionnaire (Appendix 1), which was also back translated for validation into English prior to dissemination. The study was made available online from February to July 2011, and was hosted in a secure server at the King's College (London) Institute of Psychiatry, which was one of the ReDNet project (www.rednetproject.eu/surveys/ita/intro) partners. The Italian survey was the first questionnaire in Italy on NPS.

More specifically, this investigation was focused on the level of knowledge and preferred channels of communication and information on NPS amongst Italian professionals.

The anonymous questionnaire items revolved around mainly three NPS-related topic areas:
a) respondents' general/personal information:
- *gender*;

- *age;*
- *employment* including *position* (e.g. psychiatrist, general practitioner, psychologist, educator, social worker, nurse, etc.) and also their *area* (e.g. ward, outpatients services, ER, etc.);
- *tenure in current position* in order to estimate their experience in the field;
- *city;*
- *availability of informatics' skills*.

b) respondents' awareness on NPS, in particular:

- *perceived level expertise*, using a 5 points Lickert's scale;
- *recognition of clients who used NPS*, including if they were following patients who used NPS, especially in the last 6 months. Proposed as a multiple choice the question suggested an option "*I don't know*" in order to distinguish different cases;
- *most identified NPS*; the question enlisted 16 substances popular at the time of the survey, including a fake compound (E3PO) as false positive; for each NPS there were 3 options (*Yes / No / Never heard*) in order to explore the knowledge of single substances and their popularity amongst health professionals;
- awareness of NPS intake associated risks exploring the relevancy to their activity, the psychopathological risks related to NPS and the key-points to understand a novel compounds (e.g. providing a technical folder);
- professionals' clinical experience about treatment and management of NPS intake.

c) respondents' preferred tools to gather information relating to NPS, estimating the available and classic sources (e.g. scientific literature) but also exploring novel and online resources (e.g. newsletters, websites, youtube videos).

A research protocol was developed and ethics approval for the Italian study was granted by University of Padova (Protocol Number n.0008266) on January 2011. This was in addition to the approval for the ReDNet project by the Ethics Committee the Universities of Hertfordshire-UK (Protocol Number n. PHAEC/10-42).
Each health professional was asked to formally consent to participate to the survey. All responses were anonymous and confidential, were securely stored, and were made accessible only to members of the research team. The study complied with both the UK Data Protection Act 1998 and with the Italian law for data privacy (Legislative Decree 196/03).

*Differences and peculiarities of the Italian survey: the psychopathological risk of NPS*

The Italian survey presented a peculiar cluster of questions differing from the English version (Appendix 1 and 2; Table 13); this section of the questionnaire was custom designed to explore NPS psychopathological issues considering clinicians experience in their field.

**Table 13: Question n 13 in the Italian survey [translated].**

| "According to your clinical experience, the NPS intake …" | |
|---|---|
| **… follows the occurrence of anxiety disorders in patients/clients** | 1-2-3-4-5 |
| **… follows the occurrence of mood disorders in patients/clients** | 1-2-3-4-5 |

| | |
|---|---|
| **.. .should be considered as a risk factor for the occurrence of mood and anxiety disorders** | 1-2-3-4-5 |
| **... is associated with a personality disorder diagnosis in patients/clients** | 1-2-3-4-5 |
| | |
| **... should be considered as a risk factor in the onset of schizophrenia/psychotic disorders** | 1-2-3-4-5 |
| **... should be considered as a triggering factor in cases of psychomotor agitation** | 1-2-3-4-5 |
| **... could complicate treatment and management of the acute medical/psychiatric presentations** | 1-2-3-4-5 |
| **... make the emergency protocols/guidelines somehow ineffective/inappropriate** | 1-2-3-4-5 |

*The Italian online survey: recruitment*

Recruitment started in Northern Italy and involved 8 Departments of Psychiatry, 9 Departements of Addiction, 4 Departments of Paediatrics and 3 Emergency Services. Each director was contacted and the whole study was presented, including a Word version of the questionnaire, UK and Italian ethics approvals and a brief description of the ReDNet project. If the main director agreed to participate in the survey each health professional of department received an email containing an introduction to ReDNet and a direct link to the online survey. Using this methodology the research team did not collect single health professionals' emails, protecting form traceability.
From July 2011 the survey was also distributed via the network of the Italian Anti-Drugs Department (Dipartimento Politiche Antidroga-DPA), which allowed contact with all the Departments of Addiction in Italy.
A paper version of the questionnaire was also made available to both those who did not have access to the Internet requesting to complete the survey and to a wide range of professionals who were in attendance of specific conferences or ReDNet dissemination events and seminars in the country.

**Table 14: Recruitment of the online survey in Italy.**

| | **Cities** |
|---|---|
| Departments of psychiatry | Padova (1-2-3 Servizio), Vicenza, Monselice, Chioggia, Dolo, Asolo |
| Departments of addiction (Ser.D) | Padova, Monselice, Camposampiero, Conegliano, Verona, Legnago, Treviso, Rovigo, Chioggia. |
| Emergency Services | Padova, Treviso, Monselice |
| Departments of Paediatrics | Padova, Vicenza, Conegliano, Treviso |
| Italian Departments of Addiction (Ser.D) | National soil through DPA Network |

All responses were anonymous and treated as confidential, securely stored electronically, made accessible only to members of the research team. The study complied with both the UK Data Protection Act 1998 and with the Italian law for data privacy (Legislative Decree 196/03). At the end of the questionnaire, each participant was asked whether they were happy to be contacted for future research professionals and, if so, to provide their e-mail addresses. This personal information was stored separately, in a different database, in order again to prevent traceability.

*Statistical analysis*
Data were processed with SPSS v.16 and made use of means and descriptive analysis for**:** the description of the sample; levels of respondents; their NPS expertise and knowledge; and clinical opinion. The chi square/Fisher's exact test was used to compare the different departments' data, whilst ANOVA, with Bonferroni correction, was used to evaluate possible differences in the number of NPS misusers assessed.

*Ethics and privacy*
The survey was approved by the Ethics Committee of both the Universities of Hertfordshire-UK (Protocol Number n. PHAEC/10-42) and Padova-I (Protocol Number n.0008266). Each health professional was asked to formally consent to participate to the survey. All responses were anonymous and confidential, were securely stored, and were made accessible only to members of the research team. The study complied with both the UK Data Protection Act 1998 and with the Italian law for data privacy (Legislative Decree 196/03).
To be contacted for future initiatives on the field of NPS, such as conferences, surveys, online events or meeting etc. participants provided their personal or professional e-mail addresses.

**Phase 2: Evaluating the ReDNet Project**

*The design of the evaluating survey*

In order to a) explore the effectiveness of the services provided by the ReDNet project and b) inform on future development of suitable prevention models, an evaluation questionnaire was carried out a few months after the end of the project.

I personally initiated and designed the evaluation questionnaire, applied for ethics, distributed it via the ReDNet mailing list and analysed data of the results with the aim of identifying the most appreciated channels, tools and resources of the project and at understanding the impact of this project amongst registered professionals. In the 2013 the ReDNet project was ended but I was still collaborating at distance with the University of Hertfordshire, maintaining my activity of psychiatrist in Italy.

The survey was designed and made available online with the aim of receiving feedbacks from professionals who have been reached during ReDNet. This questionnaire was anonymous and divided in two main section revolving around two topic areas:
a) respondents' general and personal information:

- gender;
- age;
- employment (physician, psychiatrist, nurse, researcher, law enforcement officer, educator, psychologist);

- tenure in current position (in order to estimate their expertise in the field)
- country
- city.
- type of organisation (e.g. university, hospital, government or international organization, drug or alcohol team, education, police, etc.)

b) respondents' clinical expertise on NPS, in particular:

- recognition of clients who used NPS; we did not use the option "I don't know" considering the population from the ReDNet mailing list.
- relevance of NPS for their activity (using a 5 point Lickert's scale)
- use of ReDNet resources (yes / no)
- preferred ReDNet channels of information explored using a multiple choice question (*including the website, the database and the technical folders, the SMAIL system, the newsletter 'Newsbites', academic papers and scientific literature, conferences and posters, including the First International Conference on NPS, short films and communication projects and/or personal communication with the team*)
- reasons to choose ReDNet information, through a multiple choice question (*up-to-date, authoritative source, reliable, value –free and objective, fills a gap in the knowledge base, only source for this information*)
- relevancy of using ReDNet information (using a 5 point Lickert's scale) and the use of ReDNet through a multiple choice question (*to inform policy, to inform practice and treatment, to educate themselves, to inform service commissioning, to develop resources, to provide context for research, to programme planning/monitoring/evaluation, for advocacy*)
- the differences that ReDNet made to what professional organisation do (multiple choice question: *decisions evidences based, enable services tailored to specific needs, make the organisation think differently and/or aware of new facts and emerging issues, provide a base line against which progress can be monitored, update policies*)

The recruitment was carried out through the ReDNet mailing list, sending a brief presentation of the questionnaire and a link containing the specific URL (http://goo.gl/vvIiP).

The survey was available online from April 2013 to July 2013 using the cost-effective freeware Google Drive technology. The survey targeted professionals across Europe, especially within the partnership of the ReDNet project (e.g. from the United Kingdom, Italy, Germany, Spain, Belgium, Poland, Hungary, and Norway). In addition, due to the international interest in NPS, the evaluating questionnaire has been offered only in English language. No further translation was proposed for the purpose of collecting feedbacks from non-European countries.

Data was processed with SPSS v.16 and made use of means and descriptive analysis for: the description of the sample; levels of respondents; their NPS expertise and knowledge. The chi square/Fisher's exact test was used to compare the different professional' data.

*A detailed evaluation for the SMAIL service*

This research project explores in details the SMAIL service, which is the most recent tool developed by the ReDNet project (May 2012) as part of its prevention activities, and specifically designed to increase awareness on NPS and to help professionals in the medical assessment phase. I personally analysed the service inquiries in the available dataset, containing SMAIL data from May 2012 to September 2013.
The SMAIL is an integrated and free SMS-Email system designed for professionals. Registered clinicians in fact are allowed to:

a) receive automatically an SMS with descriptive key points for unknown compounds texted (both as nicknames or chemical names)
b) receive instantly an email with the available and reliable information (in form of electronic fact sheets) on NPS requested
c) receive regular invitations to NPS-related events/ meetings
d) inform directly the ReDNet research team about novel trends in drug abuse.
The SMAIL system has started in May 2012, recruiting over 100 European registered users in only two months, providing a starting number of 20 factsheets and 217 drug search. This tool is still an on-going project due to the need to keep up-to-date the available technical folders and of increasing the number of fact sheets: at the present time the SMAIL service provides information covering 57 NPS, including a still large number of nicknames.

The personal information required to sign up and register to the service are: title; name; email; mobile phone number; gender; profession; country; mobile phone maker. In addition all searches carried out by SMAIL users are recorded on a distinct database, containing the follow information:

- Time and date of the search
- Type of search (SMS or email request)
- Searched word/s (string)
- Name of Substance if identified by the SMAIL
- Mobile number, email and name of the user
- Region / Country
- Mobile phone maker

All data has been electronically stored in a secure server at the University of Hertfordshire.

**Phase 3: Promoting evidence-based work in clinical practice: development of technical folders and collection of case reports**

The final phase of my work included the preparation of technical folders and clinical case studies.

I performed an extensive literature review in different databases (e.g.PsycINFO, PubMed, Medscape, Google Scholar) searching for each NPS presented here; I also monitored the web on a regular basis during the last year, with a frequency of 2 times /week. I used the methodology developed by the ReDNet project (see below) in order to report all useful information in the form of Technical Folders.

Additionally, as a psychiatrist, I encountered and initiated the study of two patients who used NPS; they arrived in the Dual Diagnosis Unit of the Italian Clinic Parco dei Tigli where I work; in this clinical context my experience with the NPS phenomenon allowed me to: a) detect the consumption of NPS b) identify an important role of NPS in their symptoms and c) offer a better help to their recovery.

*Technical Folders*

The production of technical folders is an important tool to describe novel compounds and provide information to health professionals; this approach in fact could be very helpful when a sufficient number of data are available on a new compound/product in the market, even if this is not always possible.
The methodology applied in this phase has started from the ReDNet experience in the NPS field but also integrating searched drugs from the SMAIL service:

a. Web fora searches: using popular search engines searches are carried out including specific key words for each new substance, with a full assessment of the first 100 websites and of a random samples of the 5% of the remaining websites (Research Randomizer), exclusion of all the unrelated websites, analysis of the unique websites fora, list of threads/replies/posts for each compounds and collection of the data in a password protected server. When necessary the searches are made using different languages.
b. Literature search: searches are carried out to collect and identify any information on the single NPS (e.g. PsychInfo, Pubmed, etc.).
c. SMAIL Service: searches might be suggested by registered professionals, in fact when a query produces a "No Match" answer from the SMAIL system, the team provides to retrieve any available information on the unknown compound using the 1) and 2) approaches and contacting directly the health professionals for further information on the product *in loco*.
d. Data analysis: final part of this process is the systematic collection of information for each novel compound, measured for the need of health professionals (explored in the Phase 1 and Phase 2). The technical folders organise these data under specific headings (Tab 15)

**Table 15: Headings of a Technical Folder.**

| |
|---|
| **Overview** |
| **Key points** |
| **Chemical characteristics of active constituents** |
| **Appearance** |
| **Available information on purchase price** |
| **Modalities of intake** |
| **Legal status** |
| **Current use/medicinal use** |
| **Information on recreational use/misuse in the E.U. (or elsewhere)** |
| **Use in combination with other compounds** |
| **Pharmacological characteristics** |
| **Toxicological effects** |
| **Desired psychoactive effects** |
| **Physical/medical untoward effects** |
| **Psychopathological disturbances associated with its use** |
| **Clinical advice** |
| **Related fatalities** |
| **You tube videos** |
| **Google trends** |
| **Bibliography** |
| **Sitography** |

e. All the gathered information is constantly kept up-to-date, in order to provide reliable information for each compound (e.g.: new nicknames, legal status, effects, literature, case reports, etc.), collecting and analysing also warnings received directly from the SMAIL service users.

*Case Reports*

The expanding galaxy of NPS has a relevant clinical impact and their recognition can change patients' life. The collected study cases presented here want to emphasis a) the presence of NPS during psychiatrists' clinical activities b) the importance of NPS misuse identification during clinical interview c) the needs of reliable information on these products especially when they appear on the online market (e.g. from up-to-date Technical Folders using SMAIL service) d) the difficulties in the assessment phase due to their consumption and in e) the challenge of a proper treatment in the scenario (only one clinical guidance has been produced so far) [225].

The cases presented here described patients who arrived for a detoxification and rehabilitation programme, they asked help for (classic) substance misuse but during the assessment phase in our Unit they revealed an intense consumption of novel compounds, including very recent NPS.

The reports were collected in the Dual Diagnosis Unit of the Italian Clinic Parco dei Tigli, located in Padova, in the North East of Italy (www.parcotigli.it). The Unit follows patients from all regions of Italy, offering a rehabilitation program of 30 days for alcohol, other classic substances (including cocaine, medical products such as benzodiazepines), gambling disorder, sexual addiction and also NPS, thanks to the collaboration with University of Hertfordshire. The program includes:
1) a detoxification phase
2) a psychopharmacological and psychiatric assessment
3) group and individual psychotherapy
3) psychomotor rehabilitation

For each case during hospitalization patients were investigated with

- Standard blood panel
- Toxicological exam (cocaine, alcohol, opioids, methadone, cannabis, barbiturates)
- Electrocardiography (ECG)
- Clinical interview with psychiatrist and psychologists in order to collect a full anamnesis of the case.
- The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and Axis II (SCID II) (ADD) to detect the main criteria for psychiatric diagnosis.
- Symptom Checklist 90 (SCL-90[226]) a brief self-report questionnaire to evaluate psychological symptoms. It consists of 90 items and takes 12–15 minutes to administer. SCL-90 scores on several symptom variables and global indices of pathology (Global Severity Index, GSI), which is the arithmetic mean of the items. A score of at least 1 on the GSI suggests psychopathology:
  - Mild: 1.00 – 1.49
  - Moderate: 1.50 – 1.99
  - Severe > 2.00
- Minnesota Multiphasic Personality Inventory-2 (MMPI-2), which is worldwide the most widely used and researched self-report measure of psychopathology and personality characteristics.

**Table 16: *MMPI-2's main scales[227,228].***

| *Scale* | ***Description*** |
|---|---|
| *L* | *"Lie": patient faked "good"* |
| *F* | *"Infrequency": patient faked "bad"* |
| *K* | *"Defensiveness": patient tried to denied with evasiveness answers* |
| *Hs* | *"Hypochondria": patient had concerns with bodily symptoms* |
| *D* | *"Depression": measures depressive symptoms* |
| *Hy* | *"Hysteria": measures awareness of problems and vulnerabilities* |
| *Pd* | *"Psychopathic Deviate": measures conflict, struggle, anger and respect for society's rules* |
| *MF* | *"Masculinity/Femininity": measures stereotypical masculine or feminine interests/behaviours* |
| *Pa* | *"Paranoia": measures level of trust, suspiciousness and sensitivity* |
| *Pt* | *"Psychastenia": measures worry, anxiety, tension, doubts and obsessiveness* |
| *Sc* | *"Schizophrenia": measures odd thinking and social alienation* |
| *Ma* | *"Hypomania": measures level of excitability* |
| *Si* | *"Social introversion": measures people orientation* |
| *Content Scale* | |
| *Anx* | *"Anxiety": measures tension, fears of losing mind, lack of confidence and somatic indication of anxiety* |
| *Frs* | *"Fears": measures specific fears (e.g. high places, snakes, storms, etc.)* |
| *Obs* | *"Obsessiveness": measures rumination about decisions, compulsions* |

| | |
|---|---|
| | *such as counting, obsessional thoughts.* |
| *Dep* | *"Depression": measures severe or major depression, brooding, crying easily, pessimism, suicidal ideation.* |
| *Hea* | *"Health concerns": gastrointestinal symptoms, neurological symptoms, sensory problems, dermatological problems, pain, and respiratory problems* |
| *Biz* | *"Bizarre mentation": paranoid ideation- persecutory type, ideas of reference, delusional, derealitization, and hallucinations* |
| *Ang* | *"Anger": losing self-control over aggressive impulses, irritable, impatient, physically and/or verbally abusive, and explosive.* |
| *Cyn* | *"Cynicism": Hostile, suspicious, misanthropic; feels misunderstood, distrustful, unsympathetic, selfish, grandiose, envious, and judgmental* |
| *Asp* | *"Antisocial practices": anti-authority, rationalizing and identifying with criminal behavior, admitting to antisocial or unlawful behaviors* |
| *Tpa* | *"Type A": Impatience, easily annoyed with other people who interrupt their tasks, hard driving, fast paced, task-oriented, competitive, insensitive, demanding, and racing against the clock* |
| *Lse* | *"Low self-esteem": do not like themselves, feel unattractive, clumsy, useless, inadequate, unassertive, no self-confidence, oversensitive, dependent and confused* |
| *Sod* | *"Social discomfort": introverted, shy, social avoidance, dislike of crowds or parties or group activities.* |
| *Fam* | *"Family problems": family is unsupportive, unloving, with a good deal of aggression, rejection, and hostility.* |
| *Wrk* | *"Work interference": Difficulties concentrating, anxiety, tension, pressure, lack of self-confidence, lack of support system.* |
| *Trt* | *"Negative Treatment Indicators": negative attitudes toward health care providers and treatment, pessimistic about individuals being understanding or helpful, not comfortable in self-disclosing* |
| *Supplemental scales* | |
| *APS (Addiction Potential Scale)* | *Empirically derived by selecting MMPI-2 items that differentiated alcoholics and drug abusers from psychiatric patients and normals[229].* |
| *ASA (Addiction Acknowledgement Scale)* | *Detects alcohol/drug abuse problems in the context of a general personality assessment[230].* |

The use of MMPI-2 in clinical activity, and in substance misuse in particular, has a long history, with a highly specific scientific literature: the introduction of this psychometric instrument here arrived because of my personal experience with the instrument through years, especially in difficult cases where the clinician may be in doubt about the persological profile of a patient. I suggested evaluating Alice and Marvin at the end of the recovery to better understand the cases, suggesting this test for future research even if its possible role in diagnosis or treatment of NPS clients is not in the aim of this research work.

The first case (called "*Alice*") was collected in 2014; the report describes a woman who arrived for alcohol and cocaine abuse but during recovery her anamnesis revealed an intense misuse of mephedrone and other NPS with a severe worsening which included depressive symptoms, aggressive behaviour and suicidal thoughts.

The second case (called "*Marvin*") was also collected in 2014 and describes a young man who experimented with a large amount of novel substances during his 10-years long experience as "psychonaut", developing severe psychotic symptoms due to the intense abuse of a very recent compound (alpha-PVP), which is a novel synthetic cathinone for the first time here reported as an emerging stimulant in Italy.
Again in these case reports the consumption of NPS was detected for the first time during the hospitalization, even if the patient arrived from psychiatric and/or addiction services.

**Implementing Phases 1, 2 and 3 to raise awareness on NPS**

Through its different phases, my research project aimed at implementing for the first time a "circle of information" on NPS in the attempt to raise awareness on the phenomenon and support healthcare professionals in their clinical activity. Specifically, as described in the Introduction, the information presented in: a) technical folders as well b) the scientific literature (if available), c) the web (drug fora, webstes, etc) and d) the SMAIL service could guide healthcare professionals while facing new unknown compounds, new population of clients (club drug users and psychonauts, for example) and therefore novel challenges in drug misuse, psychiatry and recovery.

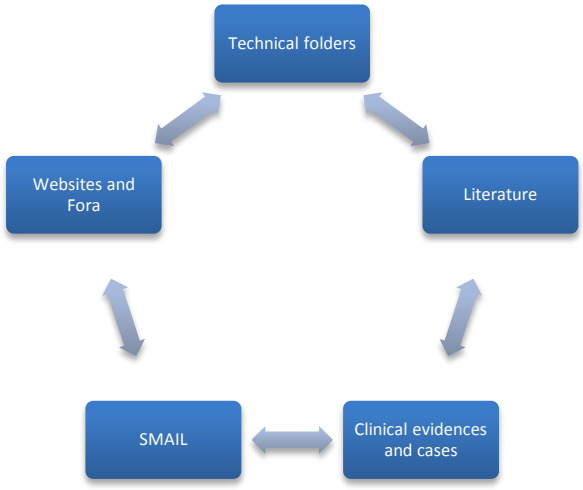



**Figure 15: Keeping a reliable and up-to-date profile through a cost-effective circle of information.**

As described in Figure 15, the expertise on NPS can be gathered from different sources, including traditional and more innovative tools. My task here was to understand the perception of the phenomenon amongst a sample of healthcare professionals (Phase 1), to describe how an European project like ReDNet could expand the awareness on NPS using technological tools (Phase 2) and to help clinicians and patients in clinical context (Phase 3).

The challenge here is to describe the NPS galaxy in the best communicative way, exploiting for example a web-interface (e.g. website), containing reliable technical information (e.g. Technical Folders), integrating the more academic data (e.g. literature and official reports) with systems able to face rapidly new trends drug abuse (e.g. SMAIL service); last but not least, the clinical confirmation of effects and risks related to NPS misuse should be recorded and illustrated (e.g. case reports) in order to be effective and incisive in helping patients.

Therefore, my task was to elucidate these different points investigating the phenomenon through different perspective during sequential years: Phase 1 probed the emerging NPS problem in a European country (Italy) in 2011, Phase 2 evaluated the innovative approach of ReDNet at the end of the project (2013) reporting registered professionals opinion and describing the use of SMAIL, while Phase 3 highlighted how the recognition of NPS (Technical Folders) means recognitions of patients (case reports) especially in a Dual Diagnosis setting (2014).
More specifically, Phase 1 targeted a group of healthcare professionals, while Phase 2 wanted to evaluate the impact of the whole ReDNet project and targeted all professionals registered to the mailing list.
This research project expressly structured in consecutive years, during which the NPS popularity arose in society, gained visibility amongst media and became an object of interest also for the scientific debate. Therefore, the need to develop quick and reliable answers to this public health

problem. Considering this framework, my work started from the clinical request of help made by patients, which found me unprepared on this new phenomenon. Consequently, searching to fill this gap in my knowledge base, I met the ReDNet initiative of University of Hertfordshire, one of the first international projects to face NPS. During my collaboration with the team, we adapted to the expansion of this galaxy following their "ever-changing" pace and designing novel solutions. The ReDNet project in particular developed new methodology for retrieving information from online sources (see Technical Folders), analysing drug fora, contributed to the scientific literature, designed novel technological services (e.g. SMAIL) with the aim at integrating traditional channels of information and innovative ones.

Designing this research work in three different phases, the objectives were to describe the lack of information regarding NPS, the clinical impact in our unprepared Health Services, in addition to evaluate and suggest the ReDNet experience and its technological tools as a model to raise awareness on novel psychoactive drugs.

## RESULTS AND DISCUSSION

### Phase 1

**Introduction:** Novel Psychoactive Substances (NPS), also known as "legal highs", are a new phenomenon across countries, and little research has been carried out in identifying the health professionals' knowledge and expertise relating to the intake of these compounds. This is particualarly true in Italy, where health services may intercept patients who used NPS and ask information on these drugs, especially in emergency setting.
**Methods:** Data presented here refer to the Italian component of the European Union – wide ReDNet project survey. This online survey was the first investigation in Italy on NPS; ad hoc questionnaire was administrated to professionals from the departments of Addiction, Psychiatry, Paediatrics and Emergency Rooms services.
**Results:** The invervieews' sample included 243 professionals, mostly from departments of Addiction (35%) and Psychiatry (28.4%). Overall, they self-reported a poor technical knowledge relating to NPS (61.3%), but judged this phenomenon highly relevant for their clinical activity. Moreover, respondents declared of not being aware if their patients presented with a previous history of NPS misuse in 27% of cases, but the 18.1% of them recognised NPS use amongst their patients.
**Discussion:** Novel psychoactive substances prevalence of misuse was not considered to be an unusual phenomenon in Italy, even if many intervieews were not able to recognise the most popular NPS at the time (e.g. Spice drugs, Mephedrone, *Salvia divinorum*). Health professionals appeared to have concerns relating to the associated medical and psychopathological risks of NPS, especially in terms of aggression/psychomotor agitation. Overall, most respondents reported the need to have better access to NPS-related reliable sources of information (e.g. technological tools as dedicted websites) in order to expand their awareness.

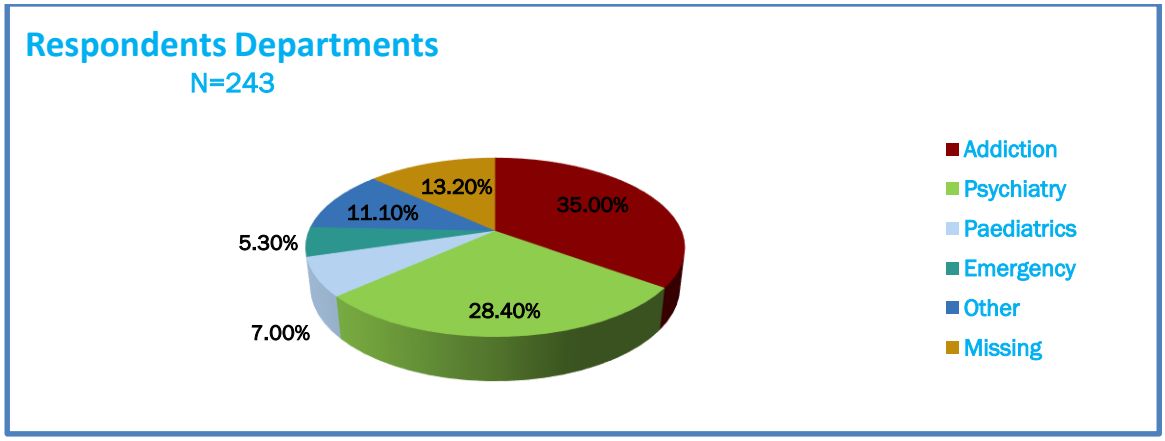
### Phase 1: Results of the online survey among health professionals

*1.1 Respondents' general and personal information*

The ReDNet survey was the first questionnaire on NPS distributed in Italy collecting a number of 243 online questionnaires amongst Italian services, 221 reached by the online recruitment and 32 by the paper version (Table 17). Interviewees had an average age of 40 years old, were women in the 60.5% of cases and declared a good expertise in their field (12.74 years old ±9.76 as tenure in their position). General data here suggested that in this online recruitment health professionals who answered to the email were long well experienced in the field but also with a relatively young age, considering the presence of residents in the sample: in fact medical doctors worked as medical specialists in the 38.7% of cases (n= 94) and secondly as medical trainees (21.4%). The survey at the same time reached nurses (12.8%), psychologists (10.7%), educators (3.7%), social workers (2.9%) and general practitioners (1.2%), too. Their informatics skills were self-rated from "intermediate" to "very good" in the 74.9% of cases, which constitutes a possible bias considering that recruitment involved in first place colleagues familiar with ICT technologies.

These Italian professionals were mainly working in the departments of either Addiction or Psychiatry (63.4%) (Figure 16), which were the main target population of the study, while Paediatrics and Emergency departments had a lower number of respondents. On one hand this response suggests that NPS phenomenon was perceived as an issue for those working in mental health and addiction, while on the other hand indicates that different services (ER and paediatrics) may have a lower interest on the matter.

Figure 16: Italian departments recruited through the online survey; n=243.




The survey investigated health professionals mostly located in North of Italy (77%; n=187), and amongst them Padova was the most represented city with 85 questionnaires compiled. Central and South of Italy were less responsive (9.9% and 7%). This different distribution probably was caused by the recruitment strategy itself, which started in Padova, where the collaborating University is located (Table 17).

Table 17: Respondents general and personal information (n= 243)

| | | | | | |
|---|---|---|---|---|---|
| **Version** | ***Online* = 221 (86.8%)** | **Paper=32 (13.2%)** | | | |
| **Gender** | Male = 92 (37.9%) | Female = 147 (60.5%) | [Missing = 1.6%] | | |
| **Age** | m= 40.36±10.8 (Range : 20 -60) | | | | |
| **Employment** | N | Percentage | | | |
| Medical specialist | 94 | 38.7% | | | |
| Medical trainee | 52 | 21.4% | | | |
| Nurse | 31 | 12.8% | | | |
| Psychologist | 26 | 10.7% | | | |
| Educators | 9 | 3.7% | | | |
| Social worker | 7 | 2.9% | | | |
| General Practitioner | 3 | 1.2% | | | |
| Other | 14 | 5.8% | | | |
| **Area** | | | | | |
| Addiction (Ser.D) | 85 | 35% | | | |
| Psychiatry | 69 | 28.4% | | | |
| Paediatrics | 17 | 7% | | | |
| Emergency departments | 13 | 5.3% | | | |
| Other | 27 | 11.1% | | | |
| [Missing] | [32] | [13.2%] | | | |
| **Average tenure in current position (years)** | m= 12.74±9.76 (Range 0-35) | | | | |
| **Geographical area (city)** | N | Percentage | | N | Percentage |
| ***North Italy*** | 187 | 77.0% | ***Padova*** | **85** | **35%** |
| | | | ***Triveneto*** | **111** | **45.7%** |

| | | | | |
|---|---|---|---|---|
| *Central Italy* | 24 | 9.9% | | |
| *South Italy* | 17 | 7.0% | | |
| [Missing] | [15] | [6.2%] | | |
| Informatics skills of the sample | | | | |
| *Poor* | *Basic* | *Intermediate* | *Good* | *Very good* |
| 3.7% (n=9) | 18.5% (n=45) | 28.8% (n=70) | 35.4% (n=86) | 10.7% (n=26) |

*1.2 Respondents' awareness on NPS*

The core of this Phase was Italian services awareness on the NPS phenomenon. The main finding is here represented by the respondents' perceived poor technical knowledge levels relating to novel compounds, with 61.3% of all respondents having self-rated their expertise as being minimal indeed (Figure 17). In fact collected results highlighted a low level of knowledge amongst the most "motivated" and probably "interested" health professionals who received the ReDNet email: therefore this percentage is probably an over-estimated rate of Italian services population knowledge.

**Figure 17: Level of expertise on NPS (n=243).**

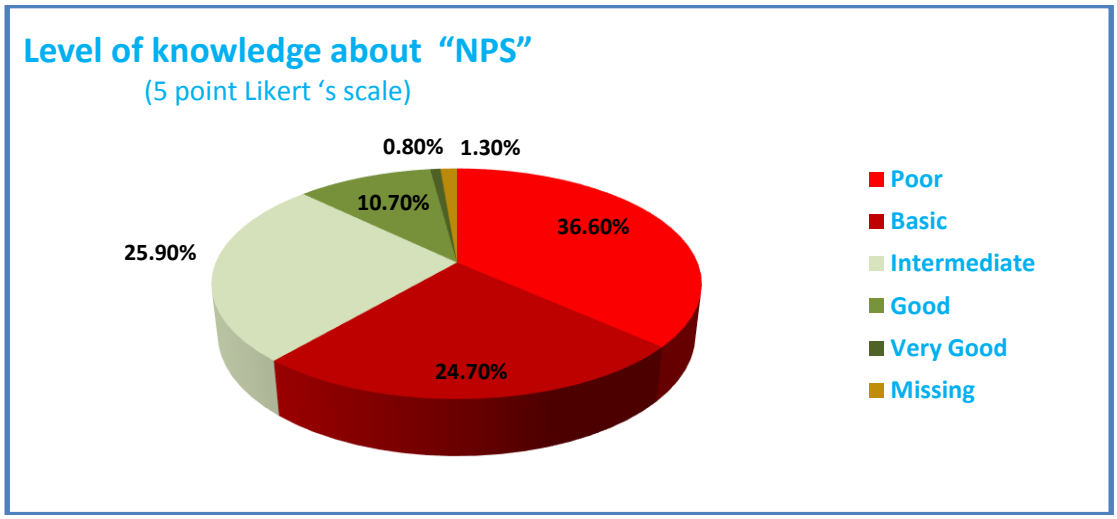



**Table 18: Respondents level of knowledge and perceived relevancy about NPS (n=243).**

| | | | | |
|---|---|---|---|---|
| Level of knowledge about NPS | | | | |
| *Poor* | *Basic* | *Intermediate* | *Good* | *Very good* |
| **36.6% (n=89)** | **24.7% (n=60)** | 25.9% (n=63) | 10.7% (n=26) | 0.8% (n=2) |
| Relevancy of NPS in your clinical activity | | | | |

| Not relevant | Poorly relevant | Relevant | Quite relevant | Very relevant |
|---|---|---|---|---|
| 0.4% (n=1) | 3% (n=7) | 22.7% (n=53) | 32.2% (n=75) | 41.2% (n=96) |

Considering clients using NPS a large amount of respondents seemed not to follow these users in their clinical activity (47.30%), while the 18.1% of interviewees recognised the misuse of novel compounds by their patients. A relevant point here is that over a quarter of clinicians (26.7%) did not even know if their clients were using NPS, meaning that they did not ask about novel compounds in clients' anamnesis (Figure 18). More specifically this percentage was particularly higher if we consider psychiatrist and professionals in the ER departments (41.8% and 30.8%): even if limited by size of the sample, this trend should be a cause of concern. In Italy, in fact, psychiatrists are called to operate in emergency setting where these compounds could produce severe psychopathological effects with risk of errors in the assessment: therefore as literature highlighted[57,156,209,231,232] the misdiagnosis can lead to important consequences, especially in the management of patients. Although the diffusion of NPS in Europe was a fairly recent issue at the time, this questionnaire confirmed that the NPS intake should not be considered an unusual event, probing that 18% of the health professionals had been here involved in the care of misusers (Table 19).

Figure 18: Awareness on Novel Psychoactive Substances (NPS) amongst the sample (n=243).

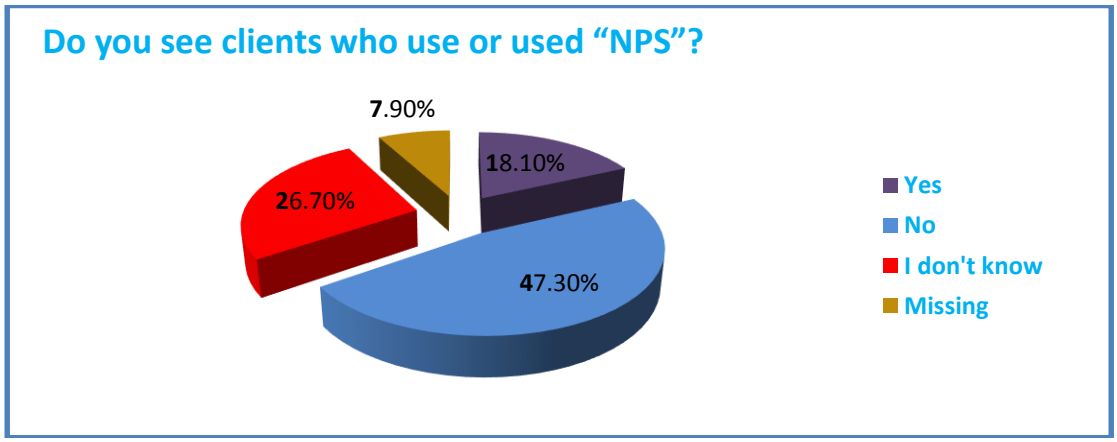



Table 19: Awareness on NPS amongst the sample and within areas (n=243).

| Do you see clients who use or used NPS? | n | Percentage | Within Areas | n | Percentage |
|---|---|---|---|---|---|
| Yes | 44 | 18.1% | Addiction (N=84) | 25 | 29.8% |
| | | | Psychiatry (N=67) | 11 | 16.4% |
| | | | Emergency (N=13) | 1 | 7.7% |
| | | | Paediatrics (N=17) | 0 | 0% |
| No | 115 | 47.3% | Addiction (N=84) | 40 | 47.6% |
| | | | Psychiatry (N=67) | 26 | 38.8% |
| | | | Emergency (N=13) | 8 | 61.5% |
| | | | Paediatrics (N=17) | 12 | 70.6% |
| I don't know | 65 | 26.7% | Addiction (N=84) | 16 | 19% |
| | | | Psychiatry (N=67) | 28 | 41.8% |

| | | | | | |
|---|---|---|---|---|---|
| | | | Emergency (N=13) | 4 | 30.8% |
| | | | Paediatrics (N=17) | 5 | 29.4% |

According to their clinical experience, interviewees were also asked to recognise single NPS popular in national soil: the question permitted healthcare professionals to identify each compound as "misused", "not misused" or completely "unknown". The most recognised NPS in Italy seems to be Spice drugs' class, mephedrone, Salvia divinorum and GHB, while other compounds (e.g. BZP, MDPV) were less identified (Figure 19) and the most recent substances at the time (e.g. 6-APB) were largely unknown.

Also here it is important to observe that respondents to the survey were probably the most informed and curious on NPS, so even if data can not describe level of knowledge of healthcare professionals who did not answer, could be a reasonable consideration that their expertise was probably lower.

It seems important to notice that in Italy:

a) Spice drugs (synthetic cannabinoids) and mephedrone were officially banned by DPA in 2010[233].
b) Salvia divinorum was scheduled in 2005[234].
c) GHB is still used in clinical settings as a medical product for alcohol withdrawal (Alcover) [235,236].

So, at the time of this survey, the most recognised abused NPS should be already "well-known" by health professionals, who in large part instead never heard about their name. This is particularly true into psychiatric services: data analysis revealed that 23.8% did not know synthetic cannabimimetics, 38.1% did not recognise mephedrone and 45.5% of them never heard about the most "ancient" compound of the list, *Salvia divinorum*. Even department of addiction seemed not to declare a great confidence with NPS: Kratom for example was not recognised by 50% of them, and in similar percentage MDPV (45.5%) (Table 20).

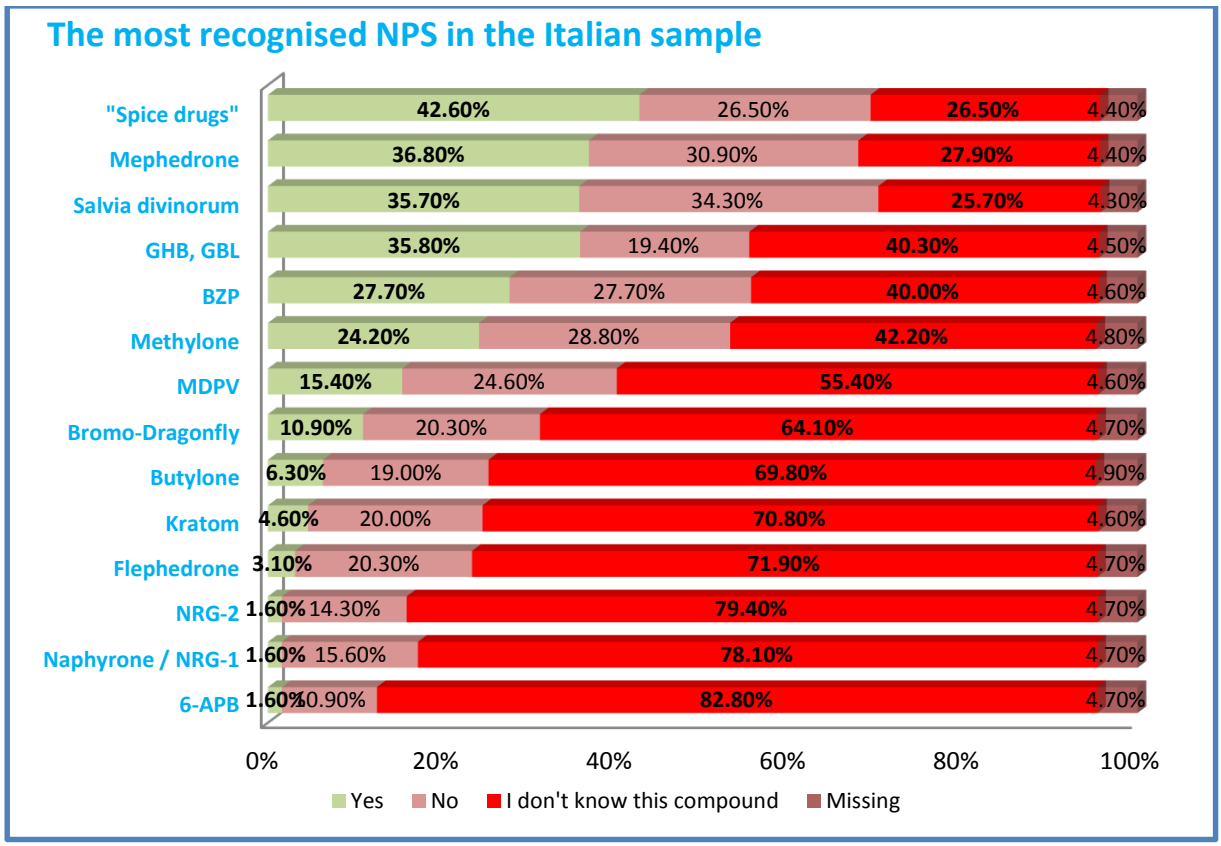



Figure 19: The most identified NPS in Italy.

**Table 20: Knowledge about single NPS.**

| | Yes | No | I don't know this compound | In Department of | | |
|---|---|---|---|---|---|---|
| | | | | Psychiatry | Addiction | |
| **Spice drugs** | 42.6% | 26.5% | 26.5% | 23.8% | 8.0% | $\chi^2$=8.52 p=.004 |
| **Mephedrone** | 36.8% | 30.9% | 27.9% | 38.1% | 8.0% | $\chi^2$=6.21 p=.010 |
| **Salvia divinorum** | 35.7% | 34.3% | 25.7% | 45.5% | 0.0% | $\chi^2$=15.84 p=.001 |
| **GHB, GBL** | 35.8% | 19.4% | 40.3% | 60.0% | 8.0% | $\chi^2$= p=.000 |
| **MDPV** | 15.4% | 24.6% | 55.4% | 61.9% | 45.5% | ns |
| **Kratom** | 4.6% | 20.0% | 70.8% | 90.5% | 50.0% | $\chi^2$=8.08 p=.003 |

At the same time Italian clinicians appeared worried about this new phenomenon, first of all defining NPS from "relevant" to "very relevant" to their clinical work in the 96.1% of cases (Table 18); moreover specific questions on clinical concerns about novel compounds revealed that interviewees seemed to highlight the long-standing problem of the "dual diagnosis", emphasising a serious concern for patients' use on these products (Figure 20).

Specifically according to the respondents' clinical experience, the use of NPS should be considered an important risk factor, which may be especially associated with aggression/psychomotor agitation (75.7%) and with an increased difficulty in the assessment phase (75.7%) as well as in the treatment and management, especially in ER settings.

Furthermore, most interviewees (71.2%) expressed concern about the potential risk of acute psychotic episodes in association with the intake of NPS: this preoccupation was confirmed in recent literature especially for synthetic cathinones, cannabinoids and new phenethylamines[9,127,182,204]. Almost all 61% of interviewees suggested also a possible role of NPS as a triggering factor for mood/anxiety disorders. Conversely (Figure 20), according to respectively 41% and 36% of interviewees, NPS intake may be preceded by mood, and anxiety disorders, raising the risk of self-medication and self-treatment, which is an important issue of these online products easily available online[219]. In confirming the above, recent evidence from the UK and Italy seems to suggest the existence of high prevalence levels of psychiatric co-morbidity, associated with a poor clinical prognosis, amongst NPS users[85,237].

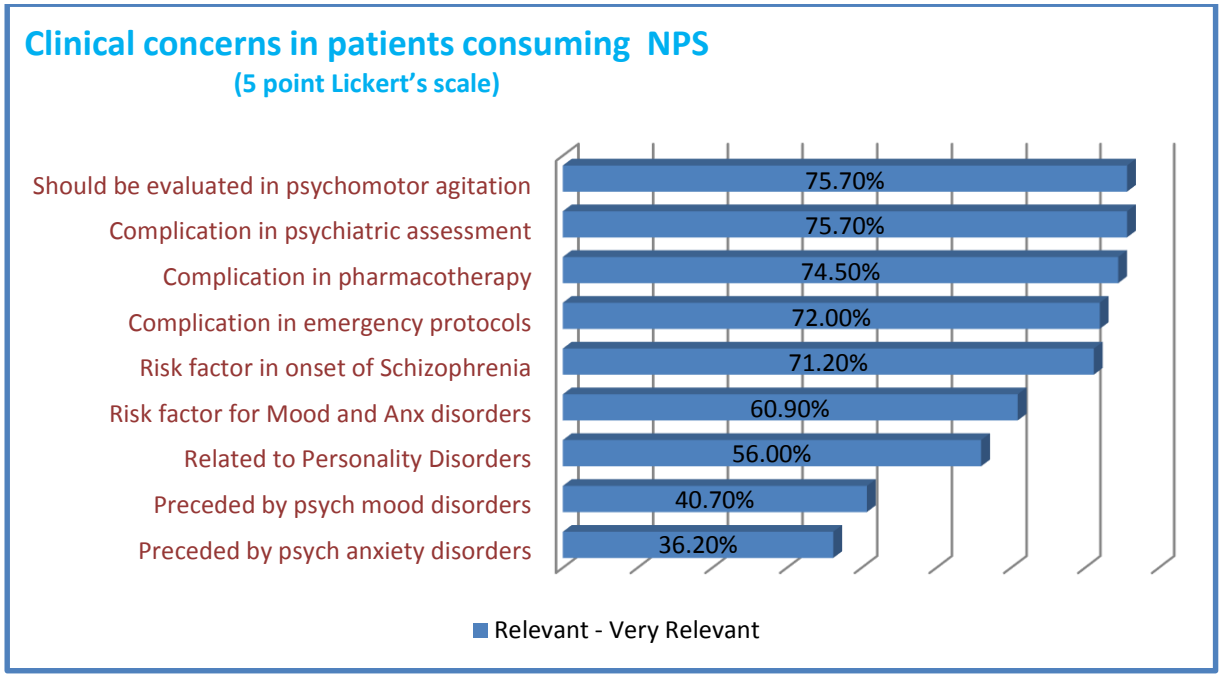



**Figure 20: Medical risk in the use of NPS according with interviewees' clinical expertise; n=243.**

*1.3 Respondents' preferred tools to gather information on NPS*

Very briefly, most (96%) Italian health professionals were here concerned about the possible risks associated with NPS intake, and this was considered to be a very relevant factor to their everyday practice. Overall, according to the survey results, they felt that they were not in receipt of any regular NPS-related updates. In fact, only less than a quarter of them had access to NPS-related data (n=72), quoting both the web (23%) and the scientific literature (21%) as the main sources, even if these sources could be either not be peer-reviewed and/or not quickly updated. An issue of NPS galaxy in fact is the rapid diffusion of these compounds and consequent difficulty to keep pace with their expansion.

**Table 21: Main sources of information on NPS in the Italian sample (n=72) [Multiple choice].**

| Source | Percentage |
|---|---|
| **Websites** | 23% |
| **Scientific literature** | 20.6% |
| **Conferences** | 18.5% |
| **Email** | 16% |
| **Newsletters** | 14.8% |
| **Patients** | 11.1% |
| **Colleagues** | 9.1% |
| **Media** | 3.7% |
| **Social network** | 1.6% |
| **SMS** | 0.4% |

However most (95.5%) interviewees reported the need for more information about NPS. Italian healthcare professionals chose rapid and technological options for dissemination, including: emails (70%); access to dedicated websites (51.9%); newsletters (40.3%); access to appropriate Second Life events (34.2%) and Facebook pages (14%). Important to notice here that clinicians seemed to select as preferential many ICT tools experimented by the ReDNet project such as the website (www.rednetproject.eu), the Facebook page (www.facebook.com/pages/ReDNet-Research-Project), the Twitter account, but also both more innovative (SecondLife) and classic (e.g. Conferences)

events. SecondLife in particular was a novel solution developed by the ReDNet team, which permitted confrontation on NPS data easily and rapidly amongst experts across the world: this virtual environment in fact allowed the meeting of professionals and researchers thorough their "avatar" in real time, from their own offices and Universities, with the aim to share information on NPS. Results here showed that this very innovative experience was well appreciated by Italian healthcare professionals.
Furthermore, this data was a key point for the development of innovative solutions, such as the SMAIL service, with the aim of providing reliable information on NPS.

**Table 22 Preferred channels of information on NPS (n=213) [Multiple choice].**

| Source | Percentage |
|---|---|
| **Email** | 70% |
| **Websites** | 51.9% |
| **Newsletter** | 40.3% |
| **Second Life Events** | 34.2% |
| **Facebook** | 14% |
| **Conferences** | 7.8% |
| **SMS** | 3.3% |

*1.4 Limits*

As described the respondents from Paediatrics and Emergency Room services were little represented, and the entire sample of the survey size was limited. Health professionals recruited were mainly from Northern Italy, probably because the study started from University of Padova as an Italian centre for the survey. There is no information on professionals who received and/or not completed the questionnaire and therefore survey's representativeness is not known. Considering the methodology adopted here, we can suppose a very low response in general by services and Departements of Addiction in particular. This fact would suggest different interpretations: a) contacted healthcare professionals did not consider relevant NPS to their field b) they did not have the time to complete the survey (this could be the case of busy services, like Emergency Units) c) the distribution of the survey was not efficient. Hence, the results of the survey should be treated with caution, even if they probably overestimated the interest for the phenomenon amogst services. Another selection bias is the online platform used here may have self-selected professionals confident with ICT tools. Future studied should investigate Central and Southern regions of Italy as well as Emergency and Paediatrics health services.

*1.5 Final considerations on Phase 1*

Through the online survey for healthcare professionals we explored Italian services expertise on NPS, reaching medical specialists, resident physicians and other figures working on Departments of Psychiatry and Addiction. Other important areas for this phenomenon (e.g. emergency medicine and paediatrics) seemed less sensitive even if NPS had acute presentation and involved young people. Results from this Phase suggested anyway a good interest in the subject amongst interviewees but a self-declared poor understanding of novel compounds: the 26.7% of respondents did not know if their patients used NPS, and that is particularly true for psychiatrists of the sample (41.8%). This result is important and concerning because:

a) according to literature psychiatrists have a risk not to recognise properly (classic) drug misuse in emergency setting[209] and they may have a higher risk with novel compounds.

b) level of knowledge was minimal in general for most of the sample (61.3%), and due to the limits of the questionnaire recruitment this data is over-estimated for the whole professionals' population.
c) expertise was quite low also for some substances already banned/warned at time of the survey (mephedrone and spice drugs), herbal plants like Salvia divinorum (banned in Italy in 2005) and Kratom, but also for medical products like GHB currently used for alcohol withdrawal by the same Departments of Addiction[235,236].

In Phase 3 (*Alice* and *Marvin* case reports) we will describe severe repercussions on patients when novel substances are not properly recognised.

On the other hand, respondents considered NPS as a very relevant problem in their clinical activities, especially in terms of psychomotor agitation and aggressiveness (75.7%), errors in the assessment (75.7%), treatment and management of these clients, mainly in emergency settings where unpredictable acute symptoms may appear. Last but not least health professionals considered NPS an important trigger for psychotic disorders (71.2%), an issue recently confirmed in peer-reviewed literature and international reports[9].

Finally, participants seemed not to have reliable source of information on new substances and they all requested for more up-to-date and rapid channels, suggesting innovative and technological tools (such as email, websites, newsletter, social networking, SMS) in order to expand their own expertise. The ReDNet project aim was to help European professionals not to be "unprepared explorers" using these novel channels of dissemination[5,197].

**Phase 2**

**Introduction:** Novel Psychoactive Substances have been targeted by the Recreational Drugs European Network (ReDNet), a project led by the University of Hertfordshire with the aim at studying these new compounds, improving the level of information and exploring innovative communication technologies (e.g. dedicated website, Facebook page, the first automated SMS-Email Service [SMAIL]). The ReDNet initiative was funded by European Union, supported by the UNESCO Chair in Information and Computer Ethics, and involved ten research Centres in eight countries. The project was active from April 2010 and June 2012.
**Methods:** An online survey was created to evaluate the effectiveness of the ReDNet project and its technological dissemination tools. The anonymous questionnaire targeted professionals registered to the ReDNet mailinglist, investigating their general/personal information (e.g. employment, country) and expertise on NPS (e.g. recognition of clients, use of ReDNet resources). Further, an analysis of the SMAIL service was carried out in order to understand the clinical impact of this pilot innovative tool.
**Results:** The evaluating survey reached 270 registered professionals, mostly physicians (n=142), researchers (n=48), other healthcare and various professional profiles (e.g. law and enforcement officers, journalists), too. Interviewees were both from EU (Italy, 53%; UK, 18%) and non-EU regions (e.g. Australia, Canada, USA, Ghana, Kenya), and declared a good recognition of NPS users during their activity (61.1%). The ReDNet website was the most appreciated resource (48.5%) together with more classic ones (e.g. academic literature, 34.1%). The whole project itself was judged able to educate (52.2%) and expand awareness on NPS (48.2%), up-to-date (46.7) and reliable (43.3%) in its provided information. Until September 2013 the SMAIL database revealed 557 searches, inquired by health professionals using their personal smartphone: the main finding here was the high number of unknown compounds/nicknames available in the drug market (47.5%) which were not possible to identify.
**Discussion:** The ReDNet initiative was evaluated by the sample as a reliable and trustworthy project, able to provide up-to-date information on NPS. The results suggest that ReDNet was used internationally by different professional groups (e.g. physicians, researchers and others) who were able to identify and recognise NPS users during their activity. Respondents used both classic (e.g. academic papers, conferences) and innovative channels of information (e.g. website and Facebook page, SMAIL service, mailing list) to expand their knowledge and expertise in the field. In that regard, the use of the SMAIL system to identify compounds seems to be promising and cost-effectiveness, even if this tool must be adjusted (e.g. new nicknames, novel products, classic substances).

**Phase 2: Evaluation of preventive services developed by the ReDNet project, including first SMAIL results**

*2.1 The evaluating survey: general information on the sample*

The evaluating survey reached all the health professionals registered to the ReDNet mailing list (N=998), and in 4 months (from April 2013 to July 2013) two hundred and seventy questionnaires were completed (RR= 27%). The small response rate here could be related to the short period of time in which the survey was available, and even if we could not describe reasons of no responders, all data should be interpreted with caution. The gender distribution of the interviewees was well balanced (54% were male professionals and 46% female, Figure 21), with an average age of 46.8 (SD=± 10.4) years and average length in their profession of 13.2 (SD=± 9.3) years, showing a good level of expertise in their field(s).

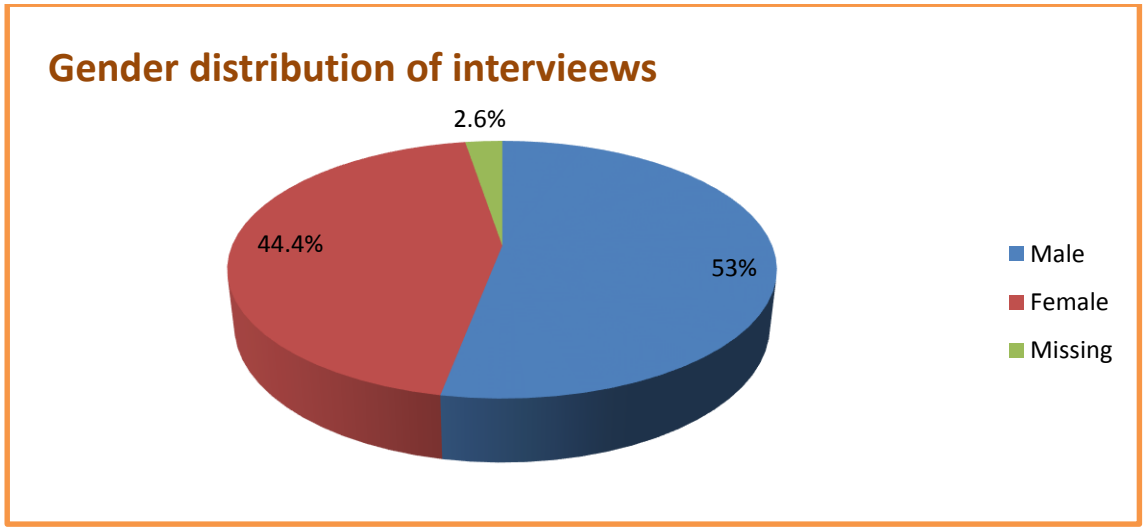



Figure 21: Gender distribution in the evaluating online survey on ReDNet activities; n=270.

Table 23: General information of the sample; n=270.

| | | | |
|---|---|---|---|
| Gender | Male = 143 (53%) | Female = 120 (44,4%) | Missing = 7 (2,6%) |
| Age | m= 46.8 (SD=± 10.4) years [Range 22 to 75] | | |
| Average tenure in current position | m= 13.2 (SD=± 9.3) years [Range 1 to 43] | | |
| RR | 27% | | |

The questionnaire intercepted different professional profiles: physicians and healthcare professionals, academic researchers and other figures (Figure 22).
First of all, interviewees (Figure 22) were mostly physicians (n= 142), and psychiatrists in particular (n=97). This was an interesting result considering the poor acquaintance with NPS declared by Italian health professionals in the previously discussed survey on novel compounds (see Phase 1 results), even if two samples were not comparable. Considering their main nationalities, the high number of psychiatrists seems to suggest among these clinicians an increased interest related to NPS, which has spread in recent years and were well studied at European level by ReDNet collaboration. On the other hand, it may just be an artefact: registered interviewees could be recruited at events, national and international congresses on the subject, promoted by the project itself.
Furthermore, there was also a relevant number of researchers/professionals involved in research (n=48) underlining an important academic interest in this fast growing field: as a matter of fact when NPS phenomenon arise with the case of mephedrone, scientific literature and research in general were mostly unprepared, with few dedicated centres: during the period of ReDNet activities the interest in this field grew on national and international level[238-240].
At the same time many other healthcare professionals answered the survey (e.g. educators, psychologists, nurses, drug workers, social workers): they were all figures directly involved with patients/clients. These results could suggest that many figures may have interest on novel compounds, not only and exclusively physicians but all professionals working in services and contributing to identify and manage NPS users[241].
On the other hand, amongst the interviewees there were also different professional profiles such as forensics professionals and toxicologists, government professionals, law and enforcement officers (Figure 22). This heterogeneity strongly confirmed the relevance of a multidisciplinary approach to face properly the NPS galaxy including several issues such as toxicological characterization, legal

controversy and police activity[7,57]. Twenty-one respondents declared an "other occupation", including chemist, pharmacist, journalist and students.

Analysing these results on sample general information, could be discussed the opportunity, in future initiatives, of disseminating on NPS with specific aims, strategies and even languages adapted to each professional profile, even including young people and the new population of users.

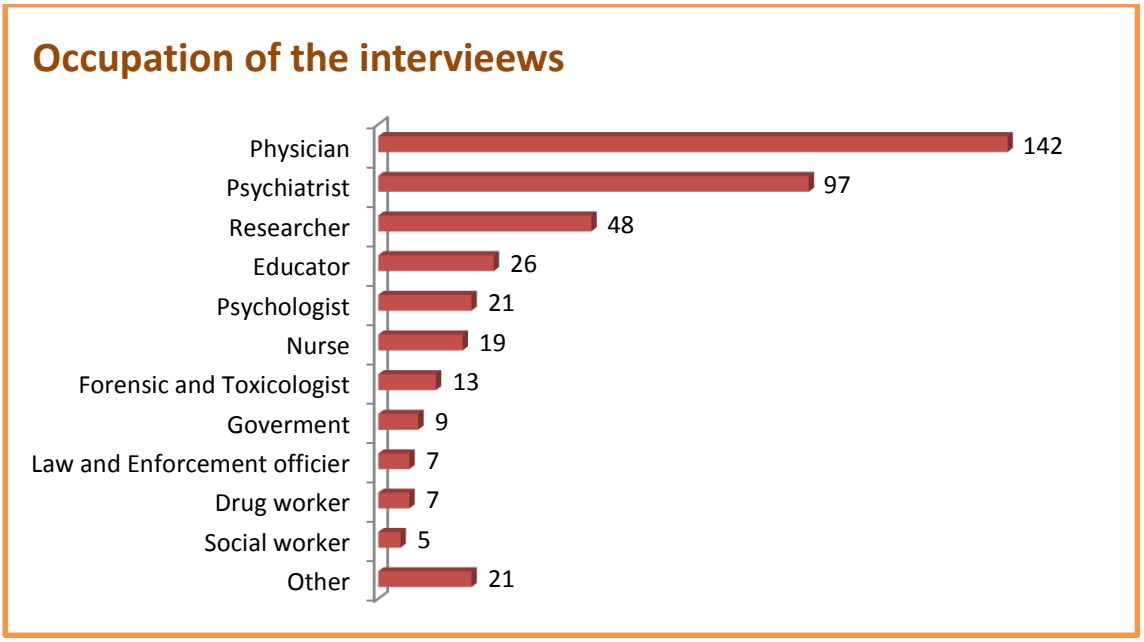



Figure 22: Professional positions of respondents; n=270 [Multiple choice].

Table 24: Occupations of the sample; n=270.

| Occupation | n | Percentage |
|---|---|---|
| Physician | 142 | 52.6% |
| Psychiatrist | 97 | 36% |
| Researcher | 48 | 17.8% |
| Educator | 26 | 9.6% |
| Psychologist | 21 | 7.8% |
| Nurse | 19 | 7% |
| Forensic and toxicologist | 13 | 4.8% |
| Governmental professional | 9 | 3.3% |
| Law and enforcement officer | 7 | 2.6% |
| Drug worker | 7 | 2.6% |
| Social worker | 5 | 1.9% |

| | | |
|---|---|---|
| Other | 21 | 7.8% |

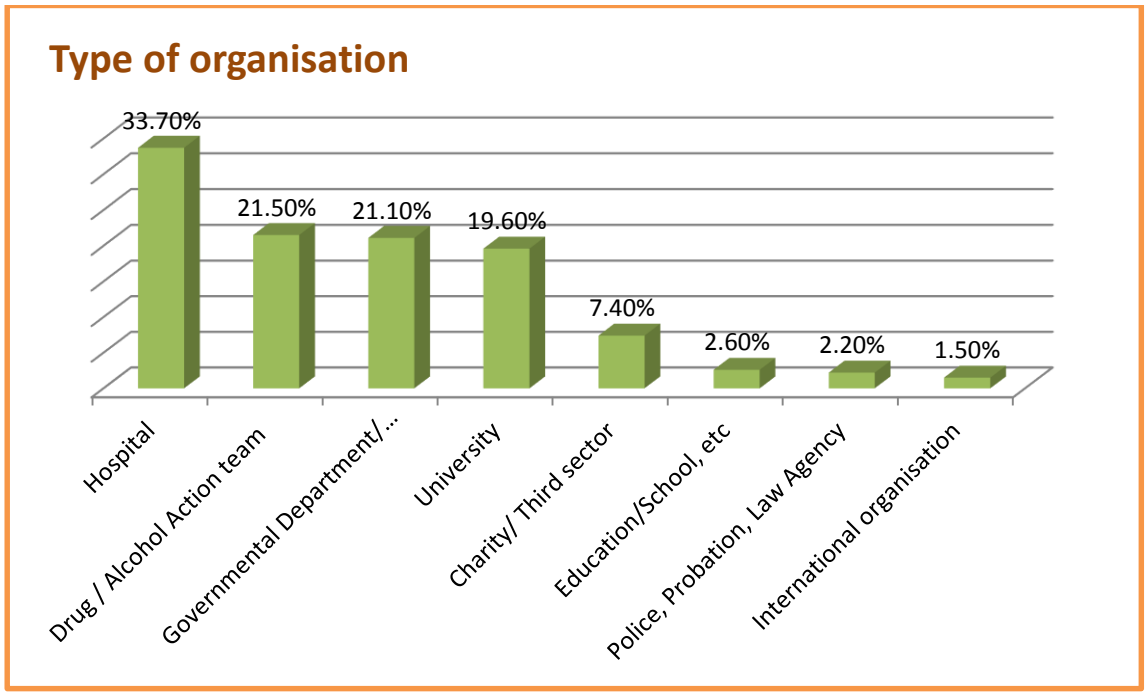



**Figure 24: Type of organisation/employment of the sample; n=270 [Multiple choice].**

Coherently, professionals who answered to the ReDNet survey (Figure 24) worked not only for hospitals (33.7%) and drug/alcohol action teams (21.5%) but also for governmental agencies and in academia. These results confirmed an interest both from the "clinical" perspective (psychiatrists in hospital/drug action team) and from the "research" field (Universities and government departments) highlighting a converging concern for novel compounds. Other sectors seem to be less represented, even if they cover crucial areas for the NPS phenomenon. Again this may lead to consider developing different strategies to increase their attendance at further prevention projects.

Interviewees were both from European and non - EU regions. Specifically, respondents were from 22 different counties (Figure 23), mostly Italy (53%) and the UK (18%). Many other European countries answered (e.g. Spain; Germany; Norway; etc.) but also Australia, Canada, USA, Ghana, Kenya, Mexico and Taiwan. This geographical distribution is probably related to a) the fast growing phenomenon of NPS on the online market, where novel compounds can be sold all over the world[57] and b) a high interest in the ReDNet approach. Originally this project started with European partnership and then expanded at international levels during its dissemination and research activity[81,82,239,240].

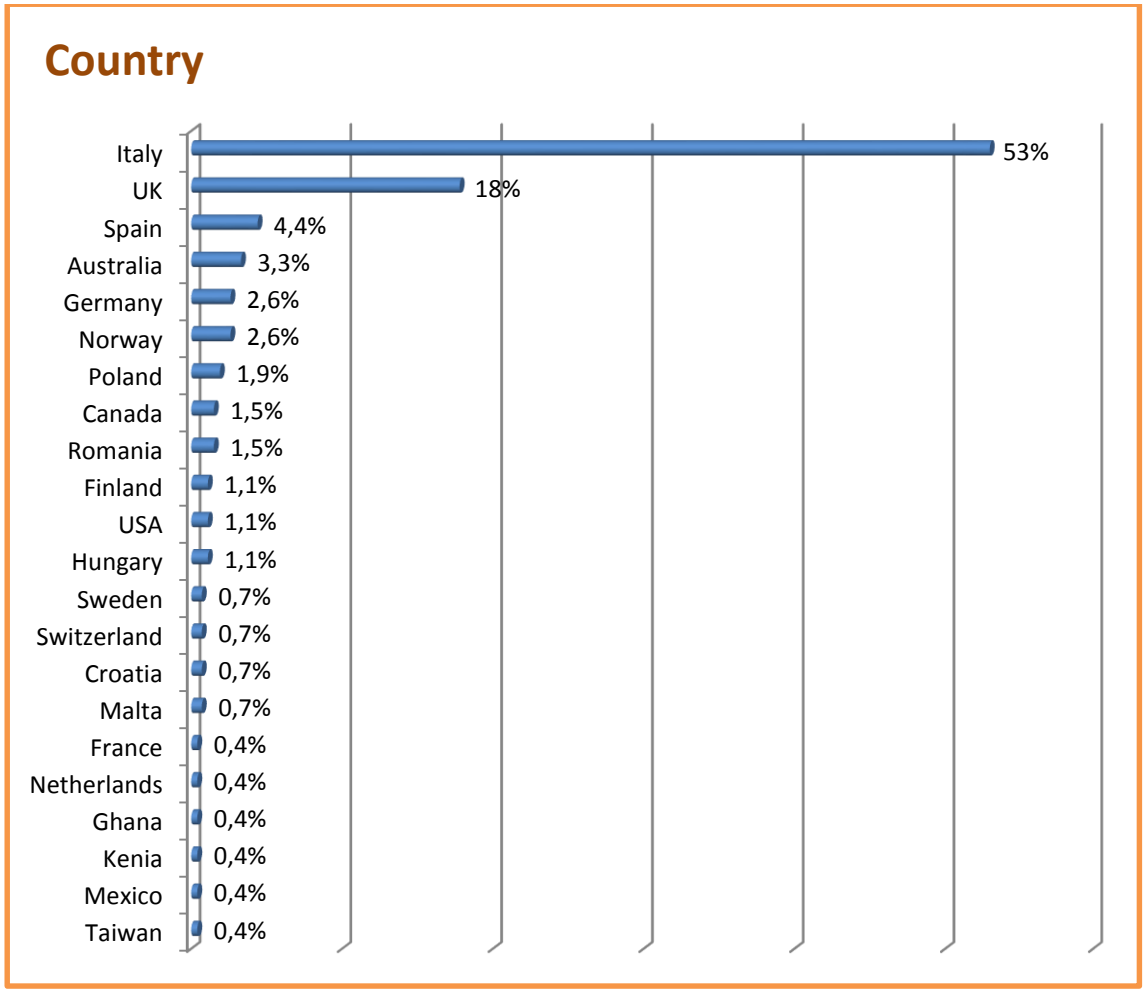



Figure 23: Nationalities recruited through the online survey; n=270.

*2.2 The evaluating survey: Novel Psychoactive Substances*

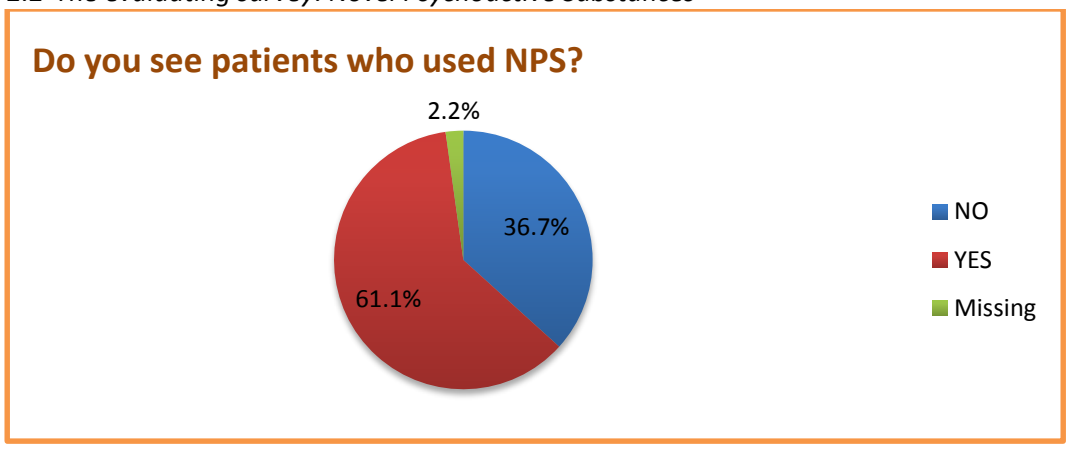



Figure 24: Recognition of clients who used NPS; n=270.

Table 25: Recognition of NPS users amongst different groups

| Do you see patients/clients who used Novel Psychoactive Substances? | | | |
|---|---|---|---|
| | Yes | No | Missing |

| | | | |
|---|---|---|---|
| All sample (n=270)) | 61.1% (165) | 36.7% (99) | 2.2% (6) |
| Health professionals (n=199) | 69.6% (142) | 27.9% (57) | 2.5% (5) |
| Physicians (n=137) | 73.9% (105) | 22.5% (32) | 3.5% (5) |

An interesting result here is the significant percentage of respondents who were seeing clients with NPS misuse (Figure 24): over half of the respondents recognised these patients in their activities (61.1%). As Table 25 describes, this percentage was higher considering health professionals of the sample (medical doctors, nurses, psychologists, educators, drug workers) (69.6%); if we considered exclusively physicians they recognised use of NPS in patients in 73.9% of cases. This data stands out compared with results of the Italian survey on Phase 1, where only the 18.1% of Italian health professionals were seeing patients. As previously noted even if the two samples were not statistically comparable, numbers here suggest an increased presence (or more probably identification) of NPS amongst health professionals recruited by the project.
Consistently the interviewees judged from "relevant" to "very relevant" the understanding of NPS for their work (Figure 25) confirming here the high value of the subject for clinicians.

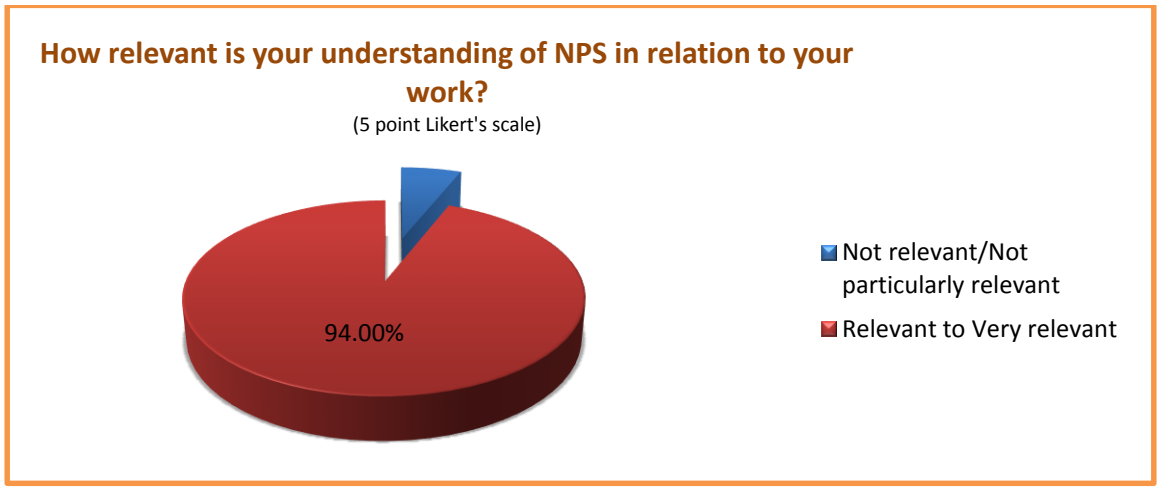



**Figure 25: Relevance of NPS in respondent's work; n=270.**

*2.3 The evaluating survey: ReDNet resources*

Professionals declared here to appreciate ReDNet channels, in particular both a) informatics tools (such as the website and newsletter) and b) more classic resources (for example scientific papers and conferences).
More specifically responses from the evaluating survey demonstrated that for a high number (48.5%) of the sample (Figure 26) the most used ReDNet tool was its website, underlining how nowadays the role of informatics tools to obtain reliable information on NPS reveal to be incisive for them. For example according to data collected in the Phase 1, only less than a quarter of health professionals had access to NPS-related data, therefore the development of a reliable website in order to disseminate news, events, Technical Folders and scientific papers is worth noting.

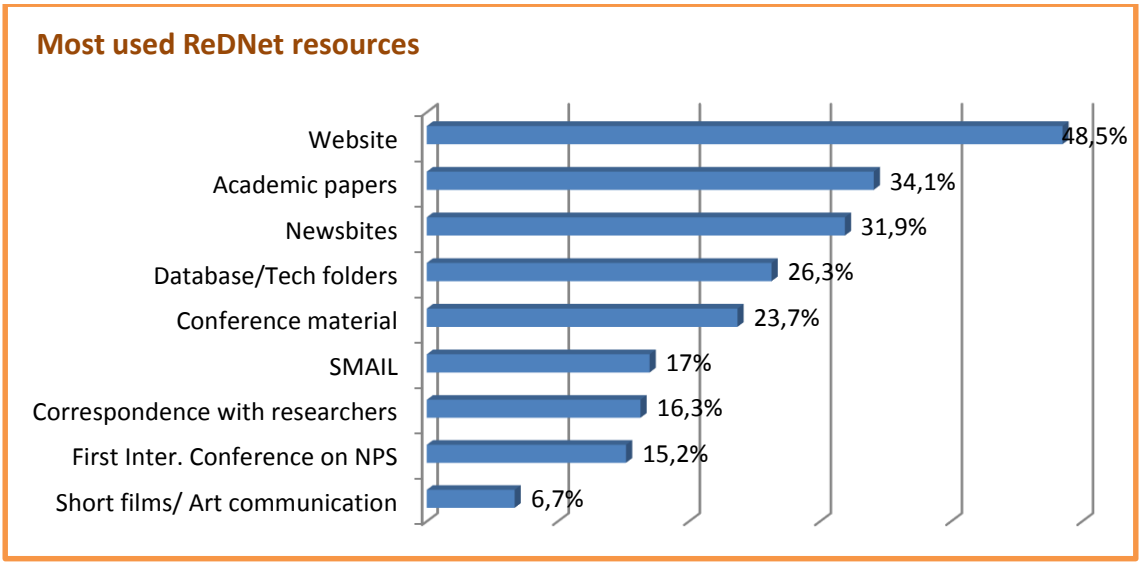



Figure 26: The most used ReDNet resources by the interviewees; n=270 [Multiple choice].

Secondly, the evaluation survey (Figure 26) confirmed the important role of academic papers as a source of information, followed by the *Newsbites* mailing list and the Technical Folders available on the ReDNet website. For 17% of the sample the SMAIL service is also regarded as a useful tool: considering that the service started only in May 2012 this result in particular seems to be significant. Interestingly conference material and particularly the First International Conference on NPS were reported as also important for professionals[238].
Overall the pertinence of all ReDNet resources was judged from "relevant to very relevant" by almost all respondents (Figure 27), which could be considered an excellent result for the project.

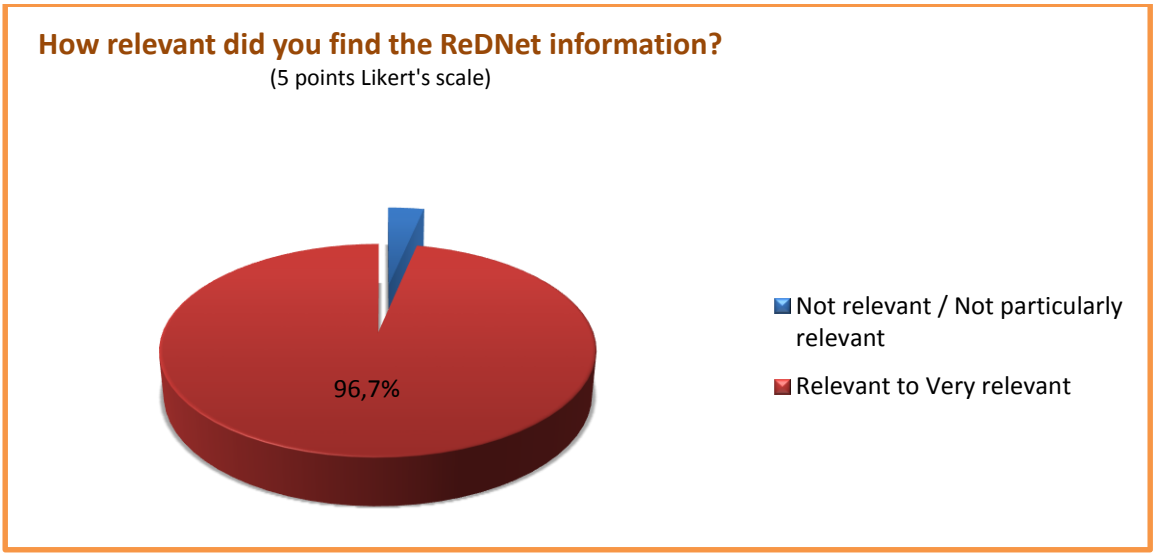



Figure 27: Relevance of ReDNet information for health professionals interviewed; n=270.

These results suggested the main role of a website as a first channel of dissemination. As a matter of fact ReDNet interactive website (www.redenetproject.eu) was the key medium by which results and update news were disseminated: the main page was translated into all languages covered by the project partners and was embedded with a number of multimedia features, including an internal database (wikiserver) for project partners, links to social networking applications, downloads,

contribute function and links to the range of project activities[223]. By June 2012, the number of visitors (per month/last month) was 1,176, with an average value of over 1,000 for the last six months of the project. Overall, the website has been visited by 16.567 people, with 998 people having registered on the mailing list. A project Facebook page connected with the main site was launched in April 2010 (Figure 29) and was kept updated with regular posts on various substance misuse issues as well as project activity updates. By June 2012, it counted 400 'likes' from individuals from 20 different countries including the USA, Australia and Costa Rica. The official ReDNet mailing list "NewsBites" (Figure 30) was a weekly email bulletin aiming to provide regular up-to-date NewsBites on NPS from around the word. It was distributed to over 900 subscribers each week. It was designed in two main sections, one summarising/highlighting the latest peer-review papers and the other selected general media coverage of NPS, promoting also other project activities.


**Figure 28: ReDNet website.**


**Figure 29: ReDNet Facebook page.**


**Figure 30: ReDNet Newsbites.**

So we can observe here that healthcare professionals and researchers used mainly the website and ICT tools but on the other hand they highlighted as useful resources (Figure 26) academic literature (34.1%) and specific up-to-date technical folders on NPS (26.3%) produced by the research group but also the attendance at conferences (23.7%).
This is a key point explored and developed during ReDNet project: an integration of such different dissemination tools.
During its activity in fact one of the primary modes of dissemination occurred via both formal and informal conference presentations, seminars and strategic meetings across Europe.
Just for the record, a total of 134 presentations were given by the ReDNet group at national and international conferences/seminars, including the experimentation of SecondLife events[242] which provided a virtual environment where to disseminate contents, attempt to online meetings and discuss with colleagues from all over the world.
The ReDNet project, in cooperation with the EMCDDA, successfully co-organised the first international conference on Novel Psychoactive Substances (NPS) 'The Ever-Changing World of Psychoactive Drugs' conference, which was held on 12-13 March 2012 in Budapest, Hungary[238]. The international perspective was emphasised, with the participation of about 60 guest speakers, who submitted an abstract and were selected by the scientific organising committee. The event was attended by 250 participants from countries around the world, including Europe, Japan, Australia and Iran and it was streamed live online. The ReDNet group and the EMCDDA planned also the next NPS conference at the University of Swansea, UK, in September 2013 (www.novelpsychoactivesubstances.eu), exploring streaming of main interventions, online "twittering" and a new interactive website[239].

### *2.4 The evaluating survey: effectiveness of ReDNet project*

The ReDNet initiative seemed to support registered professionals and their organisations both from clinical and academic perspective. Probably because of professions within the sample (Figure 22) the uses of ReDNet tools were mainly directed to (Figure 31):
(a) self-education and informal practice,
(b) supply information for research.

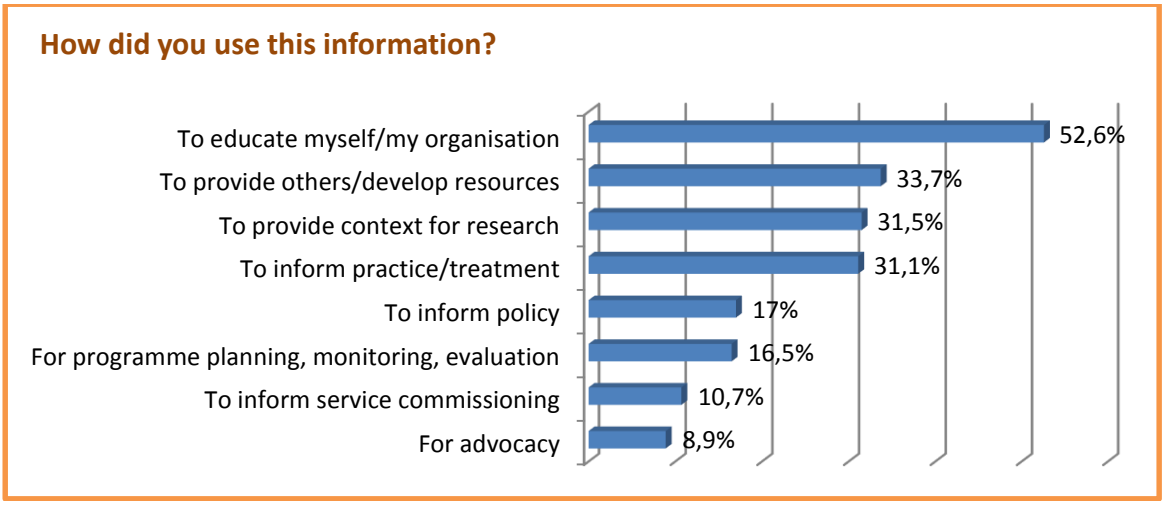



Figure 31: The use of ReDNet information; n=270 [Multiple choice].

In fact the most important use of ReDNet information for interviewees was to increase knowledge of NPS (52.6%) and then to provide or develop resources on this topic (33.7%). These results were in accordance with the well-known lack of information on novel compounds, the emergence of the phenomenon in recent years and the difficulty of health services[2,4,10,20,66,80,163,213]. In third position there was the need of providing context for research (31.5%) then informing practice and treatment (31.1%). Other uses (inform policy; planning and monitoring; informing service commissioning; advocacy) were not common probably because more related to other less well-represented professionals.

As a matter of fact interviewees selected ReDNet information and data (Figure 32) because they were judged up-to date (46.7%), filled a gap of knowledge-base (43.3%) being reliable (39.6%). The ReDNet project was also perceived as authoritative in the field (35.4%) and objective (34.4%) (Figure 32), which is a particularly distinctive result.

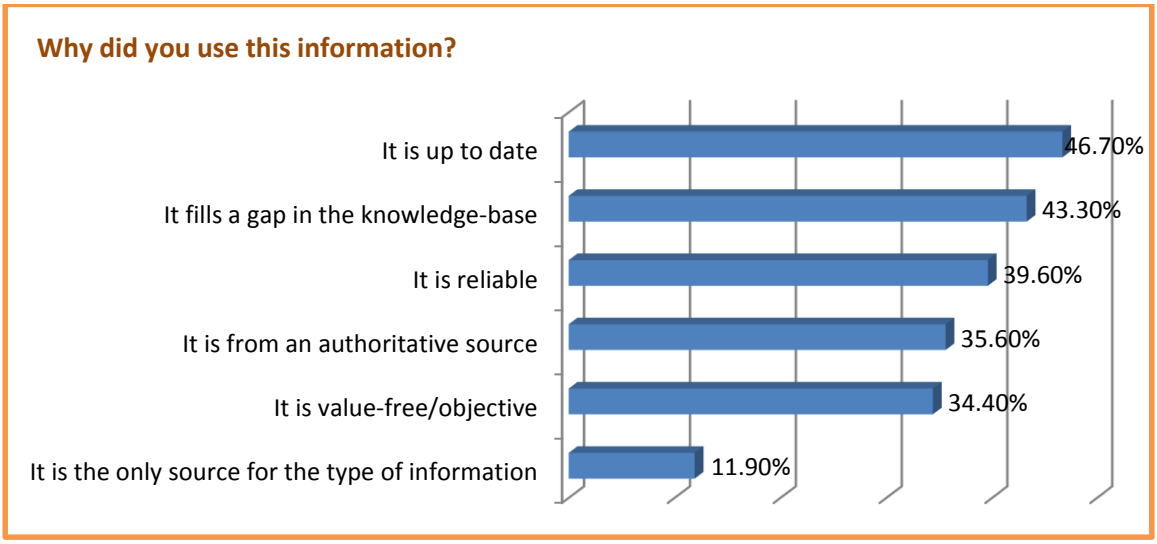



Figure 32: Reasons for using ReDNet information; n=270 [Multiple choice].


**Figure 33: Advantages in using ReDNet information; n=270 [Multiple choice].**

Finally, the ReDNet project made a difference amongst different professionals and their own organisation, contributing to improving their practice.
In fact, for almost half (48.5%) of respondents this information made them aware of new emerging issues (Figure 33) and for 34.1% oriented evidence-based decisions (Figure 33). From a clinical perspective this was a key result for prevention: due to the absence of clinical guidelines and/or protocols at the time[225], health professionals reported using ReDNet information in their clinical activities, probably because they were aware that NPS are an overlooked risk factor.

### *2.5 Limits*

The questionnaire size was fairly limited here, with a very modest response rate (27%) considering the whole ReDNet mailing list. Furthermore no information on other professionals who received and/or not completed the questionnaire was available, so the survey's representativeness is not known. Again this could suggest suggest different interpretations: a) registred professionals who did not answer did not consider ReDNet relevant to their field b) they did not have the time to complete the survey, considering for example that it was available only for four months c) the distribution of the survey was not efficient. Another bias was that the online questionnaire may have self-selected professionals who were confident with ICT tools. Some figures and operators (social workers, law and enforcement officer, pharmacists, journalists, etc.) were poorly represented as well as many countries reached by the project (see Figure 23). Future approaches should design appropriate communication strategy for these groups who declared an interest in NPS.

### *2.6 The evaluating survey: final considerations*

Two hundred and seventy professionals evaluated here the ReDNet project, in particular healthcare professionals and researchers in the field of drug misuse; they were mostly from Italy, UK and European countries, even if results suggested that the ReDNet approach and events probably reached many other regions (including Australia, Canada and USA). Especially amongst recruited

physicians identification and recognition of NPS in their everyday activity was high (73.9%), meaning that the project probably extended their familiarity with this phenomenon. The most appreciated channel of dissemination was the website (48.5%), which provided access to academic papers, news, technical folders, conference material: professionals seemed to use ICT tools and classic educational resources, both provided and experimented by the ReDNet team during its activity. The integration of those channels was used to a) self educate (52.6%) and b) supply information for research on novel compounds field (33.7%), where data must be up-to-date and reliable, filling a gap in the knowledge-base of healthcare professionals: as a matter of fact ReDNet was considered a objective (34.4%) and authoritative source (35.6%) by respondents.

### *2.7 First results from the SMAIL database (May 2012 – September 2013): general information*

During the last period of activity ReDNet initiative promoted the SMAIL service as an innovative channel to inform healthcare professionals. The SMAIL service started in May 2012 and till September 2013 recruited 122 professionals, 52% males and 48% females, with an average age of 36.96 years old (±9.3). As described in Table 26, mainly clinicians and health professionals working in the field used the service, confirming the importance of tools specifically developed to increase everyday practice. Overall the SMAIL system recorded 557 searches until September 2013. First result here was that users preferred to text their inquiries using their phone rather than email (Figure 34), suggesting the most "close at hand" option as preferential. Coherently registered health professionals accessed the service using their own personal devices (Table 27), which were specifically smartphones.

**Table 26: General information on SMAIL users; n=122 [Pilot period May 2012-September 2013].**

| | | |
|---|---|---|
| **Gender** | Male = 52% (n=64) | Female = 48% (n= 46) |
| **Age** | m= 36,96 (SD=± 9,3) years [Range 20 to 60] | |
| **Profession of SMAIL users** | Healthcare professionals | 37% (n=45) |
| | Research organisation | 25% (n=30) |
| | Operators on the field | 17% (n=21) |
| | Regulatory and government authorities | 8% (n=10) |
| | Missing | 13% (n=16) |

| Model | n | Percentage |
|---|---|---|
| IPhone | 306 | 54.9 |
| Samsung | 68 | 12.2 |
| Nokia | 25 | 4.5 |
| Sony | 18 | 3.2 |
| Blackberry | 52 | 9.3 |
| HTC | 19 | 3.4 |
| Motorola | 2 | 0.4 |
| Smartphone | 7 | 1.3 |
| Missing | 60 | 10.8 |

**Table 27: Models of smartphone used by SMAIL registered professionals in their searches.**

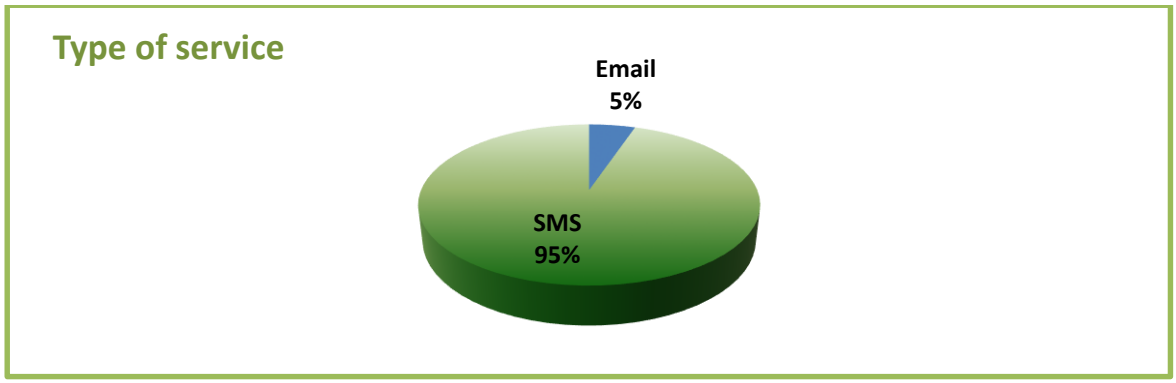



**Figure 34: The informative options of the SMAIL service; n=557.**

Even if the registered health professionals were from 22 countries, the recorded searches were texted only from 6 countries, and particularly from UK, while other regions were less well represented (Figure 35). The result might suggest a major awareness of the issue amongst English clinicians, where as many reports suggested the diffusion of NPS seems to be particularly fast growing[7,11,57].

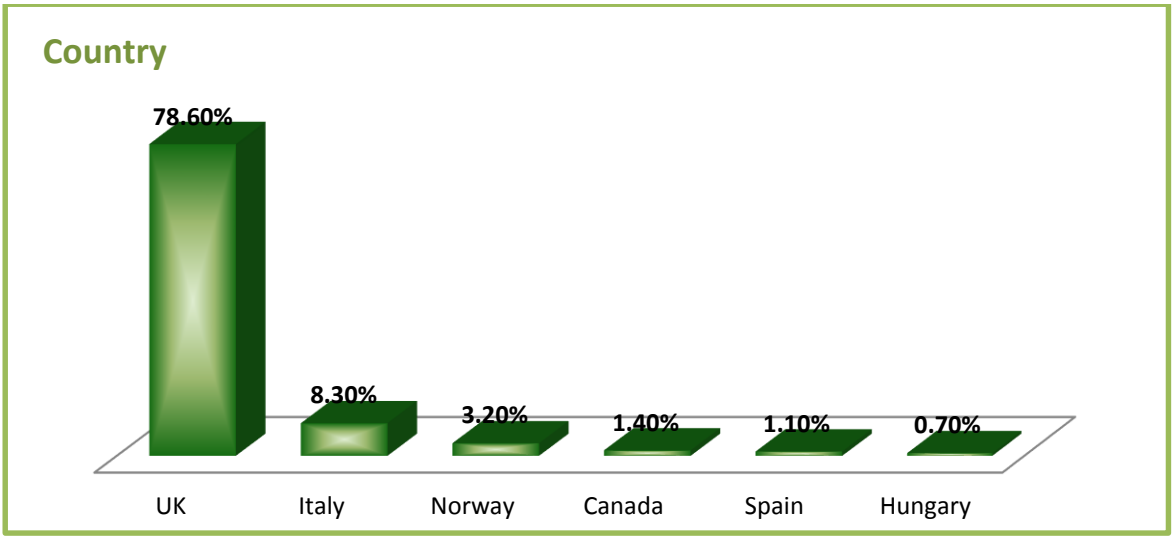



Figure 35: Geographical distribution of SMAIL searches; n=557.

*2.8 First results from the SMAIL database: NPS identification*

Nowadays the SMAIL service includes 57 factsheets on different NPS, which may be available to registered users just typing NPS chemical or known nick names; at the beginning of the pilot period the service started with 20 technical folders on the most popular novel substances, including new synthetic cathinones (e.g. mephedrone, MDPV), cannabinoids (e.g. JWH-018), phenethylamines (e.g. 2C-B, Bromo-dragonfly), ketamine-like products (e.g. methoxetamine), tryptamines, herbal and medical products (e.g. piracetam, phenazepam).

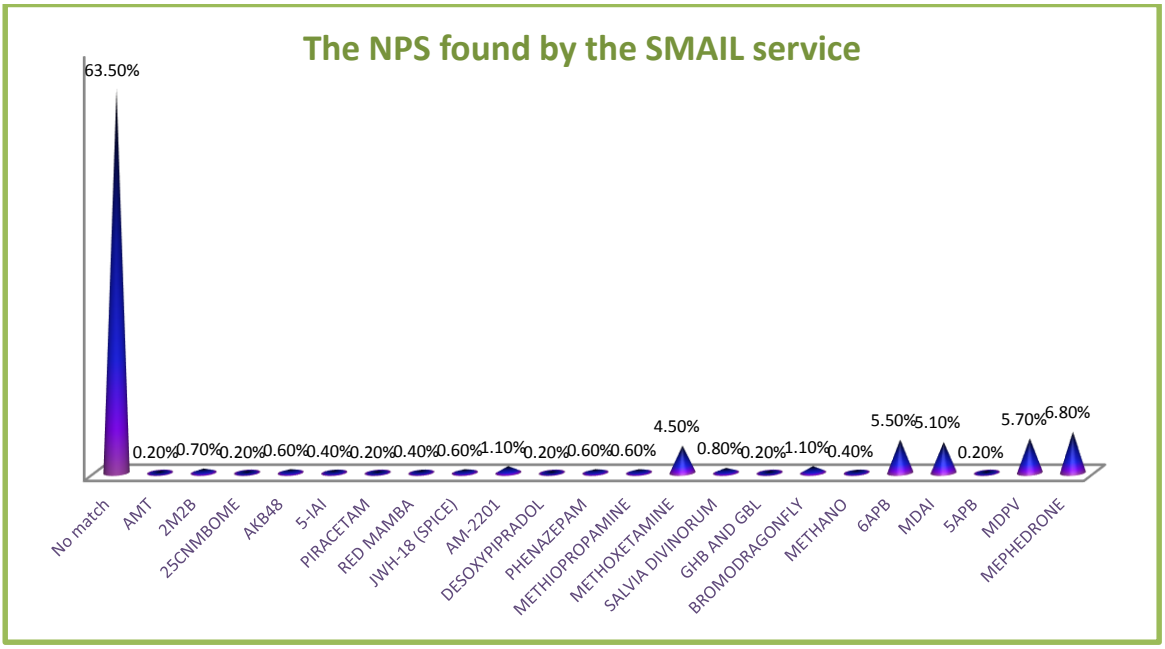



Figure 36: Novel Psychoactive Substances recognised within SMAIL database; n=557.

Table 28: Results of inquiries on SMAIL service (n=557).

| NPS identified by the SMAIL service | N | Percentage |
|---|---|---|
| NO MATCH | 299 | 63.5 |
| MEPHEDRONE | 32 | 5.7 |

| | | |
|---|---|---|
| MDPV | 27 | 4.8 |
| 5APB | 1 | 0.2 |
| MDAI | 24 | 4.3 |
| 6APB | 26 | 4.7 |
| METHANO | 2 | 0.4 |
| BROMO-DRAGONFLY | 5 | 0.9 |
| GHB AND GBL | 1 | 0.2 |
| SALVIA DIVINORUM | 4 | 0.7 |
| METHOXETAMINE | 21 | 3.8 |
| METHIOPROPAMINE | 3 | 0.5 |
| PHENAZEPAM | 3 | 0.5 |
| DESOXYPIPR | 1 | 0.2 |
| AM-2201 | 5 | 0.9 |
| JWH-018 (SPICE) | 3 | 0.5 |
| RED MAMBA | 2 | 0.4 |
| PIRACETAM | 1 | 0.2 |
| 5-IAI | 2 | 0.4 |
| AKB48 | 3 | 0.5 |
| 25C-NBOME | 1 | 0.2 |
| 2M2B | 4 | 0.7 |
| AMT | 1 | 0.2 |
| Missing | 86 | 15.4 |

As shown in Figure 36 and Table 28, healthcare professionals searched for several compounds, and in particular mephedrone (6.8%), MDPV (5.7%), 6-APB (5.5%), MDAI (5.1%) and Methoxetamine (4.5%). On the other hand in the 63.5% of queries the SMAIL service did not detect an identified or classified compound/nickname within the ReDNet database. At first sight this was a discouraging result for the project and its messaging service, but further analysis of the database tried to differentiate cases including a description of different uses of the service, SMAIL errors or inaccuracies and inquiries on new compounds.

**Table 29: Analysis of SMAIL "No Match" results (n=299).**

| Analysis of 'No Match' results | N | Percentage | |
|---|---|---|---|
| **Users Error typing** | 36 | 12,0% | *e.g.: 'B-flu' ; 'Do you know anything about Mcat?'; 'Gf'; 'SMAIL'* |
| **Unknown Compound / Nickname** | 142 | 47,5% | *e.g.: 'doob'; 'ocean snow'; 'TMA6'; 'recharge'; 'he man'; '4-MeO-AMT', 5-HTP, 'black dove', 'China white', ' dust til dawn', 'el blanco', 'ethyl-phenidate', 'exodus', 'go gaine', 'green beans', 'greengoblin', 'haze', 'hg', 'ixy', 'karma', 'king', 'loop', 'lemon, lush', 'makka', 'MAM-2201', 'mc', 'md', 'mdat', 'mig3', 'oxytocin', 'oxy', 'pink panthers', 'pink lush', 'poke', 'pulse', 'posh', 'purple bomb', 'purple ronnie', 'quiksilver', 'recharge', 'reddevil, 'red tops', 'rocket fuel', 'RoR', 'rubharb', 'skitties', 'snow white', 'solid', 'spell', 'spunout' , 'tara', 'tornado', 'voyager', 'white china', white mm', 'white widow', 'explosive'.* |
| **Compound or Nickname Added in a second time** | 36 | 12,0% | *e.g.: 'Red Mamba'; 'MCat'; 'kratom'; ' Salvia divinorum', '25CNBoMe'* |
| **SMAIL error: not recognized by SMAIL** | 34 | 11,4% | *e.g.: 'Dragon fly'; 'Nrg'; 'Mxe'* |
| **Classic Substance** | 37 | 12,4% | *e.g.: 'methadone'; 'ecstasy'; 'cocaine'; 'ketamine'; 'heroin'* |
| **Missing** | 14 | 4,7% | |

Therefore in the case of such "no match" result (Table 29), there were five main different possibilities, graphically described in Figure 37:

1- Searched substances and products were actually unknown: that is the case of new compounds newly emerged on the market, new nicknames available in streets/online market at the time of the inquiries. This preliminary result seemed to suggest that a large number of compounds were not yet identified or classified.
2- Health professionals searched for "classic" drugs: in a number of cases clinicians asked information on well-known substances including cocaine, heroin, MDMA, methadone but also some banned club drugs (like MDMA and ketamine). All these drugs were not properly considered "NPS" by the research team and the SMAIL system did not include these compounds in its database.
3- Users committed typing errors searching a compound (e.g. "B-flu" instead of "B-Fly") or mistook using the SMAIL service (e.g. texting "SMAIL" as inquiry).
4- Searched substance was not initially recognised but added in the factsheet after clinicians' warning. In this case a) some compounds/nicknames were not properly included in the SMAIL database even if popular (as the case of Salvia divinorum) or b) multiple inquiries asked information on a novel substance (e.g. 'Black mamba', 25I and C NBOMe) not yet investigated. In this case the SMAIL team produced or updated specific Technical Folders, but the database recorded previous inquiries as "no match".
5- The SMAIL system failed to recognise correctly a NPS, even if present on the ReDNet database: this errors were ascribable to inaccuracies of the system.

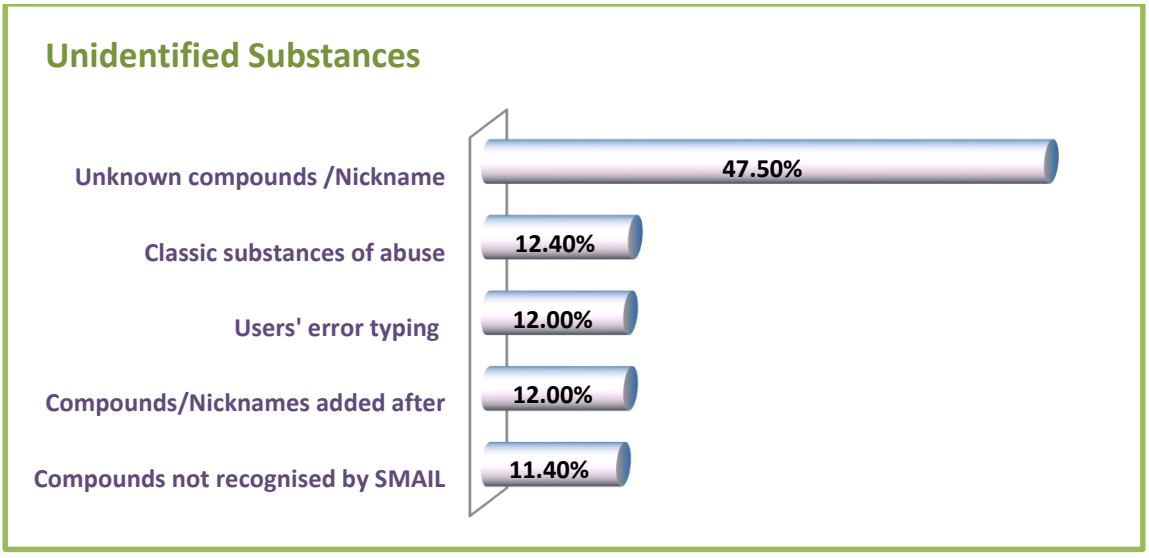



Figure 37: The unidentified compounds within the SMAIL system ("No Match").

Therefore these results firstly highlighted the difficulty of proper identification of NPS especially considering cases where only the nickname is available. Secondly underlined how a rapid service as SMAIL ought to be responsive in case of the emergence of a novel compound in the market (e.g. the cases of 'Black Mamba', 25 C and I NBOMe whose technical folder were promptly assembled and added by the team). Thirdly 12.4% of SMAIL users searched for different drugs than NPS, suggesting a low confidence with novel compounds (or substances in general). Last but not least the SMAIL system must increase its efficacy in recognising some known products or their major nicknames.
Even if they are mostly preliminary, these findings indicate that health professional who used the SMAIL service were in need of:

a) constantly upgrading information on NPS through the use of accurate Technical Folders: a compound in fact could be present online with several packaging/nicknames or may rapidly emerge on the online/street market.
b) clarification in terms of NPS definition, possibly with Technical Folder on classic substances of abuse, too.
c) corrections of some errors/biases of the SMAIL service and inaccuracies regarding its database.

### *2.9 First results from the SMAIL database: geographical distribution*

Through the SMAIL system it was also possible to diversify inquiries according to the nationality of users cell phones (Table 30). Considering for example UK (Figure 38), the most searched compounds were MDPV, 6-APB, Mephedrone, Methoxetamine and MDAI, while in Italy professionals required information especially for Mephedrone (17.1%). Other regions were less represented. Even if limited by the number of cases, these data emphasised the different geographical distribution for each NPS: in future application, the SMAIL system might also be a useful tool to map in real time this growing phenomenon.

**Table 30: Identification of NPS through the SMAIL service in UK, Italy and Norway.**

| NPS identified in UK by SMAIL | N | Percentage |
|---|---|---|
| NO MATCH | 232 | 53.0 |
| MEPHEDRONE | 22 | 5.0 |
| MDPV | 25 | 5.7 |
| 5APB | 1 | 0.2 |
| MDAI | 20 | 4.6 |
| 6APB | 22 | 5.0 |
| METHANO | 1 | 0.2 |
| BROMO-DRAGONFLY | 5 | 1.1 |
| SALVIA DIVINORUM | 4 | 0.9 |
| METHOXETAMINE | 21 | 4.8 |
| METHIOPROPAMINE | 3 | 0.7 |
| PHENAZEPAM | 2 | 0.5 |
| DESOXYPIPR | 1 | 0.2 |
| AM-2201 | 5 | 1.1 |
| JWH-018 (SPICE) | 3 | 0.7 |
| RED MAMBA | 2 | 0.5 |
| 5-IAI | 2 | 0.5 |
| AKB48 | 3 | 0.7 |
| 2M2B | 4 | 0.9 |
| AMT | 1 | 0.2 |
| Missing | 59 | 13.5 |
| Total | 438 | 100.0 |
| **NPS identified in Italy by SMAIL** | **N** | **Percentage** |
| NO MATCH | 22 | 47.8 |
| MEPHEDRONE | 6 | 13.0 |
| MDPV | 2 | 4.3 |
| MDAI | 2 | 4.3 |
| PHENAZEPAM | 1 | 2.2 |
| PIRACETAM | 1 | 2.2 |
| 25C-NBOME | 1 | 2.2 |
| Missing | 11 | 23.9 |
| Total | 46 | 100.0 |
| **NPS identified in Norway by SMAIL** | **N** | **Percentage** |
| NO MATCH | 7 | 38.9 |
| MEPHEDRONE | 1 | 5.6 |
| 6APB | 1 | 5.6 |
| GHB AND GBL | 1 | 5.6 |
| Missing | 8 | 44.4 |
| Total | 18 | 100.0 |

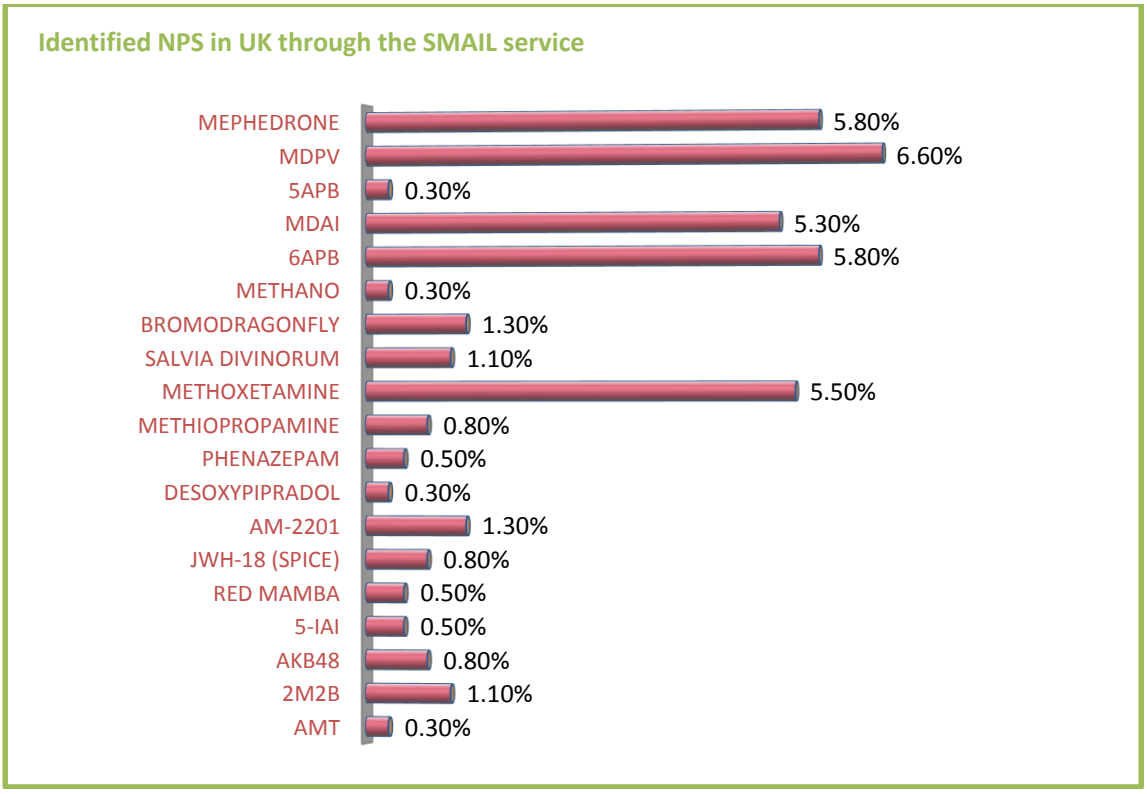



Figure 38: Identified searches in UK, n=438.

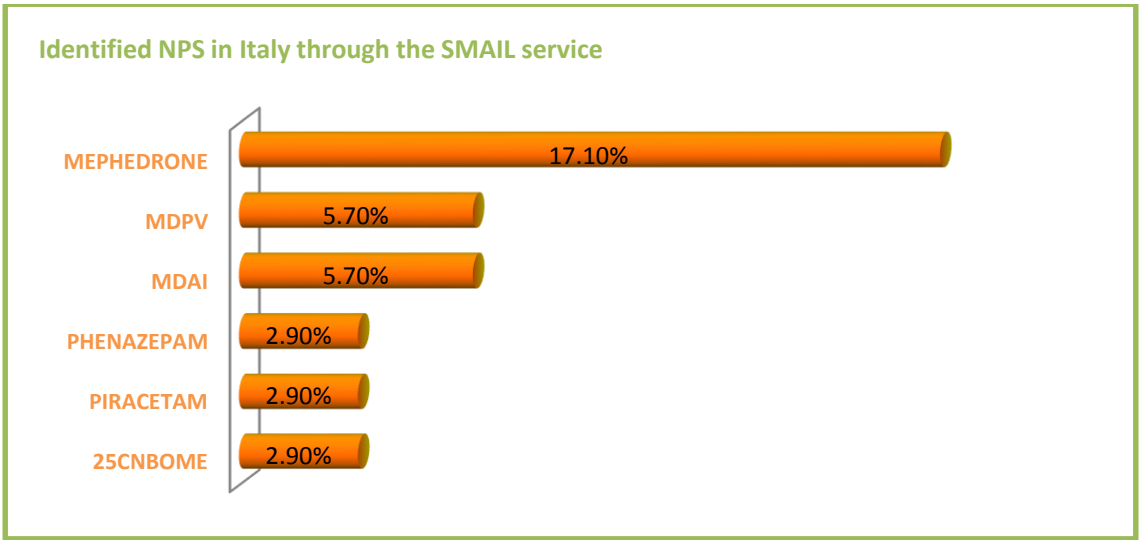



Figure 39: Identified searches in Italy, n=46.

### *2.10 First results from the SMAIL database: limits and final considerations*

The SMAIL service was promoted by ReDNet research team as a free and worldwide channel of information on NPS, intended to help clinicians in their everyday activity using text messages and emails. The analysis of the first 557 searches revealed that European health professionals accessed using their personal smartphones and preferred SMS rapidity in order to receive specific factsheets (95%). Even if preliminary and limited by size of the sample, this research project highlighted how at different levels the system might be adjusted by a) increasing number and accuracy of technical folders, including specifically new nicknames or products b) keeping up-to-date ad reliable provided information, rapidly including novel substances available online c) providing also brief factsheets on

more classic substances due to clinicians low familiarity with novel compounds d) correcting SMAIL recognition system in order to better identify NPS already included in database.
Future projects should consider this pilot system. In particular combining Internet-connected smartphone geolocation and instant-messaging application (such as iMessage, BlackBerry Messenger or the most recent WhatsApp) could be a resourceful and cost-effectiveness strategy. SMAIL could be the basis for a “close to hand” platform (for example an online application) where health professionals could a) request information, b) warn on novel products encountered during their activity and also c) mapping in real time the phenomenon.

**Phase 3**

**Introduction:** Novel Psychoactive Substances are an expanding galaxy of new compounds available as recreational drugs. The number of NPS appearing in the market has been reported more frequent than a new product every week. Considering this pace, healthcare professionals, and psychiatrists in particular, have to face a new phenomenon with unpredictable effects.
**Methods:** In this Phase we described four compounds using the methodology of ReDNet Technical Folders collecting available information and reporting under specific headings (e.g. name, modalities of intake, legal status, pharmacological characteristics, toxicological effects). Secondly we discussed two real report cases collected in clinical fields (Dual Diagnosis Unit); patients were offered with a rehabilitation program of 30 days, revealing during the hospitalisation an important misuse of NPS.
**Results:** Technical Folders described two powerful phenethylamines (Bromo-dragonfly and 25I-NBOMe), able to act at sub-milligram doses with hallucinogenic/stimulant effects; a newly misused ethno-drug (Kratom) with both stimulant and sedative properties; a recent synthetic cathinone (Alfa-PVP) appeared in the market two years ago (2013). *Alice* clinical case reported an intense consumption of mephedrone as alternative to other illicit drugs (e.g. cocaine) with related severe psychopathological consequences; the second case (*Marvin*) described psychotic symptoms due to the use of Alfa-PVP in a patient who widely explored NPS through years.
**Discussion:** The report of single NPS characteristics in the form of a Technical Folder is an effective communication and informative strategy to expand awareness on these compounds, supporting healthcare professionals in their work; on the other hand the description of clinical cases could be useful to highlight the presence of this phenomenon in the field, especially in specific populations (e.g. clubbers, psychonauts, psychiatric patients).

**Phase 3: Technical folders and case reports**

This Phase of the project describes four Technical Folders on NPS and two clinical cases, which I have personally followed while doing my research project. The clinical impact of these new substances in everyday activity as a psychiatrist was the *primum movens* of this PhD, which started as collaboration with the University of Hertfordshire and the ReDNet initiative, developed through web-monitoring novel compounds with a new and specific methodology. This investigation provided better resources to manage and help my patients.

The technical folders are: Bromo-dragonfly and 25I-NBOMe as examples of new phenethylamines; Kratom, an ethno-drug that gain popularity during recent years; alpha-PVP, a new synthetic cathinone whose technical folder was composed during the second case report presented here.

- **Technical folder: Bromo – dragonfly**
- **Technical folder: 25I- NBOMe**
- **Technical folder: Kratom**
- **Technical folder: Alpha-PVP**

The clinical studies described here are an example of the presence of NPS in our clinical activity as psychiatrists: in fact I first encountered *Alice* and *Marvin* during my activity in a Dual Diagnosis Unit in Italy, where traditional health services seem poor to recognise the phenomenon of NPS (see Phase 1). These two patients arrived in our Unit to follow a detoxification and recovery program for other more classic substances and psychiatric disturbances, but during the clinical interview their history revealed an important consumption of NPS and consequent worsening of psychopathology.

Secondly, these cases suggested a psychometric measure (MMPI-2) to define NPS users personality characteristics and also how these new patients may need specific high intensity interventions.

- **Case report n.1: "*Alice in wonderland*"**
  - Medical history
  - Previous consumption of classic substances and NPS
  - Use of mephedrone: chronology of the case
  - Assessment of the case
  - Treatment
  - Final considerations on the case

- **Case report n.2: "*Paranoid android: Marvin*"**
  - Medical history
  - Previous consumption of NPS and substances
  - Marvin and Alpha-pyrolidinopentiophenone (a-PVP)
  - Assessment of the case
  - Treatment of the case: intense interventions
  - Final considerations on the case

# BROMODRAGONFLY

## *OVERVIEW*

Chemical name: Bromo-benzodifuranyl-isopropylamine [1] [2].

Synonyms: 3C-Bromo-dragonfly; DOB dragonfly; dragonfly; B-Fly; BrDF; ABDF; Fly; Bromo-benzodifuranyl-isopropylamine; bromo-benzodifuranyl- isopropylamine [3].

Active constituents: Bromo-benzodifuranyl-isopropylamine.

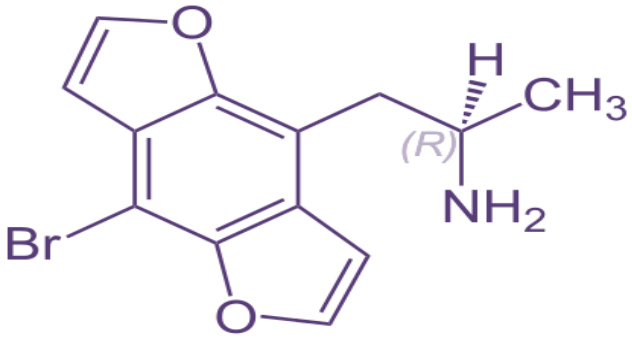



**Figure A: Chemical structure of Bromo-dragonfly.**

Type: chemical

Origin: Bromo-dragonfly (BDF) is a designed substituted phenethylamine, belonging to the benzodifurans group; this compound was synthesized in 1998 by Matthew A. Parker, during his activity in the laboratory of David E. Nichols [4]. Structurally it is related to other substances like 2C-B (4-bromo-2,5-dimethoxyphenethylamine) and DOB (2,5-dimethoxy-4-bromoamphetamine) both derived by Alexander Shulgin's studies in the 1960s. BDF was named after its superficial structural resemblance to a “dragonfly” [5] (see Figure A), together with substances belonging to the dihydrofuran series, nicknamed “FLY”. BDF was specifically designed as a novel brain research chemical acting on serotonin [6]. BDF does not have any medical use.

Status: Novel

Chronology: first reported cases of recreational use can be tracked back to 2001, even if its properties as a potent 5-HT2A receptors agonist were described in 1998 [7]. The compound appeared in Scandinavia and Denmark around 2007 with severe cases of intoxication and deaths. A few years later BDF was detected in North America and other European countries, too [8].

## *KEY POINTS*

Bromo-dragonfly is a ring-substituted phenethylamine with a long lasting (up to 3 days) hallucinogenic effect, similar to lysergic acid diethylamide (LSD). Chemically this synthetic compound belongs to the dihydrofuran class, also called “FLY” phenethylamines [8].
The three most well known compounds of this group are [9]:
A) 1-(8-Bromo-2,3,6,7-tetrahydrobenzo[1,2-b;4,5-b’]difuran-4-yl)-2-aminoethane hydrochloride (known as 2C-B-FLY)
B) 1-(8-bromo-2,3,6,7-tetrahydrobenzo[1,2-b;4,5-b’]difuran-4-yl)-2-aminopropane hydrochloride (known as 3C-B-FLY, sometimes referred to as Bromo-FLY)
C) 1-(8-bromobenzo[1,2-b;4,5-b’]difuran-4-yl)-2-aminopropane hydrochloride (known as Bromo-dragonFLY)

The nickname “FLY” is related to the chemical structure of these compounds: “wings” are composed by furanic or dihydrofuranic rings, melded in opposite positions on a central benzenic ring, resembling the form of an insect. The bromine represents the “head”, while the etilaminc or isopropylaminic group represents the “tail” [9] [10].

## CHEMICAL CHARACTERISTICS OF ACTIVE CONSTITUENTS

IUPAC name: 1-(4-Bromofuro[2,3-f][1]benzofuran-8-yl)propan-2-amine
Molecular weight: 294.14388 g/mol
Molecular formula:C13H12BrNO2
CAS Number: 10544447
[11]

## AVAILABLE INFORMATION ON PURCHASE PRICE

“Blotters” (small papers squares) were the most common forms available on the Internet starting from 2001, while nowadays BDF “pure” form (powder) can be ordered directly from chemical companies located in China [12] [13].
During these years there were two distinct "batches" of BDF which were available on the web: one more potent and one less. Since 2006, most reports indicate a dosage range for available material of 800-1800 µg while the more potent batch of product sold as Bromo-Dragonfly had a dosage range of 200-500 µg [14]. In 2005, the most potent version was sometimes called the "European" and the less potent one the "American" batch, although this distinction is not in common use. It seems likely that these two batches were not even the same chemical, but it is impossible to know [15]. Few years ago the average price was about 300 euros for 100 µg, while single dose (blotter) was about 10-30 euros [7]; however nowadays it can be sold for less than 1 euro per single gram [16].

## MODALITIES OF INTAKE:

BDF is available in various forms, including blotters (similar to lysergic acid diethylamide), but also as powder or liquid. A blotter is a small and square piece of paper, which contains a hallucinogenic compound (usually LSD); online experiences confirm that BDF is generally used in this form (and mistaken for LSD). Some reports suggest also as modalities of intake for BDF nasal insufflation or ingestion as a liquid, occasionally as tablets. Occasionally liquid formulation of BDF can be sometimes assumed onto sugar cubes. Finally, intravenous administration has also been reported [3] [15] [1]. BDF is usually colourless or white but, for example, in Australia it was also found in the form of a pink powder, paste and liquid.

**Figure A: Appearance of BDF (Source: Wikipedia).**

## LEGAL STATUS

BDF is listed as Schedule I in Oklaoma (US) and in Canada [5] [17]. In UK, Bromo-Dragonfly is widely reported by the media as being a class A drug [5], however, its legal status remains unclear [18]. At today BDF is not explicitly named in the Misuse of Drugs Act.
Other EU countries banned this new phenethylamine: Bromo-dragonfly is illegal in Sweden [19], Denmark [20], Norway [21], Romania [22], Australia [23], Finlandia [24]. In Italy this compound is not included in the banned scheduled substances [25].

## CURRENT USE / MEDICINAL USE

None. There is not a legitimate use of BDF as research, medicinal or industrial product.

## INFORMATION ON RECREATIONAL USE/ MISUSE IN THE E.U. (OR ELSEWHERE)

BDF is a synthetic and psychedelic substance, sometimes sold as LSD: both compounds are sold in the form of blotters, have an indiscernible appearance and share apparently similar effects, even if this phenethylamine induces more powerful and long-lasting effects [3] [15]. BDF as a matter of fact is used specifically as a hallucinogenic drug, similar to LSD, as has been documented in Europe, US, Canada and Australia [2] [3] [7] [8].

## USE IN COMBINATION WITH OTHER COMPOUNDS

Bromo-dragonfly is used in combination other drugs as reported by online reports [3] [15] [26] [27]:
-LSD
-Cannabis
-2C-B
-Ketamine
-Methylone
-Amphetamines
-Alprazolam
-Cocaine
-Kratom
-Alcohol

## PHARMACOLOGICAL CHARACTERISTICS

BDF pharmacological properties have been recently well investigated: studies in vitro and in animal models have shown that BDF is the most potent of the dihydrobenzofuran analogues with high affinity binding to the 5HT2A receptor [4] [28]. In particular BDF exists in two stereoisomeric forms R and S, and the first one shows more potency and more affinity to the 5HT2A receptor than S-enantiomer [29]. This data could explain the presence in the market of “batches” of different potency. During experiments in LSD-trained rats, used as an initial screen for evaluating behavioural activity and hallucinogenic potential of new molecules, BDF confirmed slightly more potent action than LSD. Furthermore, BDF showed to be a very potent ligand for cloned human 5HT2A and 5HT2C receptors and also to act at 5HT2B receptor, even ift with an affinity lower than at 5HT2A receptor [4]. In addition, some data suggest that BDF acts also as an agonist at alpha-1-adrenergic receptor. The action at both 1-adrenergic and serotonin receptor in blood vessels could explain the evidence that BDF induce severe vasoconstriction [30].

## TOXICOLOGICAL EFFECTS

Bromo-dragonfly is a very toxic drug, both according to online experiences and recent literature reports. In many cases BDF consumption required medical intervention.

More specifically, as described in case reports, subjects required medical care after recreational use of BDF principally due to induced severe vasoconstriction. The most common side effects were: tachycardia, blood hypertension, hyperpyrexia, mydriasis, psychomotor agitation, hallucinations, generalised seizures, rhabdomyolysis, respiratory difficulties, liver and kidney failure, and peripheral ischemia [31] [32]. Patients were treated with a supportive intervention using a variety of vaso-dilating drugs (such as ACE inhibitors, nitroprusside, prostacyclin analogs, glyceryl tri-nitrate, calcium channel blockers) but none of them was reported to be effective [32]. Kidney failure was treated with veno-venous hemodialis filtration while complications such as aspiration pneumonia and respiratory problems were treated with intravenous antibiotics and respiratory assistance. When they were present, agitation and psychotic symptoms were treated with intravenous benzodiazepines [34]. The extreme toxicity of BDF can be probably (but not clearly) explained by its chemical structure: a) the furanyl ring seems to impair the enzymatic clearance, resulting in a 3-days duration of "lysergic" effects [34] and b) the potency seems to increase by the presence of halogens in molecule [35].

**Table I: Bromo-dragonfly - Medical and Psychopathological Effects**

| | |
|---|---|
| **Cardiac** | Tachycardia, hypertension |
| **Neurological** | Generalized seizures, mydriasis |
| **Peripheral vascular** | Vasoconstriction, ischemia |
| **Renal** | Kidney failure |
| **Hepatic** | Liver failure |
| **Other medical** | Rhabdomyolysis, hyperpyrexia |
| **Psychoactive effects** | [with late unset] Visual hallucinations, euphoria, space alteration |

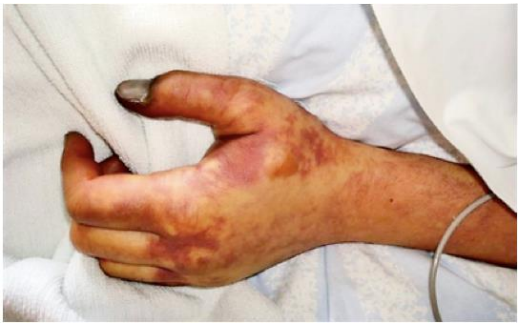


**Figure B: Necrosis observed in Swedish case (Source: Drugs-forum.com)**

## *DESIRED PSYCHOACTIVE EFFECTS*

First of all, BDF induces hallucinations due to its action as a 5-HT2A receptor agonist and it showed also mild stimulating properties. Desired effects in fact include: kaleidoscopic hallucinations, altered perception of space and time, high resolution colourful visuals, shimmering lights, increased energy, increased associative thinking, well-being, prolonged sexual pleasure, and mild euphoria [1] [15] [27]. Online users report suggest onset of psychotropic effects within 20-90 minutes of oral ingestion and within 30-60 minutes of nasal insufflation; onset of action is delayed for up to 6 hours after oral ingestion, in particular if BDF is taken on a full stomach [8]. In this circumstance the re-dose of the compound may occur: the users can assume another dose thinking that the first dose was insufficient to cause any psychotropic effects. The duration of the action is between 6-24 hours with a prolonged come down phase up to 2-3 days [8] [36].

## *PHYSICAL/ MEDICAL UNTOWARD EFFECTS*

There are numerous online reports of acute ingestion of BDF, but there have no large-scale published surveys on BDF. Self – reported experiences highlighted common side effects as headache, sweating, "twitches" in the

legs, generalized feelings of cold or hot, nausea, diarrhoea, tightness in the jaw [15]. In case studies the severe life-threating toxicity of BDF was related to the peripheral ischemia with severe skin discoloration and cyanosis of extremities and to kidney and liver failure. This effect is related probably to the high 5HT2A potency and the consequential vasoconstrictive properties [30] [33].

## PSYCHOPATHOLOGICAL DISTURBANCES ASSOCIATED WITH ITS USE

BDF misuse can induce severe psychopathological symptoms. First of all, the psychiatric effects that might occur are powerful visual and auditory hallucinations, lasting for days due to BDF potency and the high risk of re-dosing for this compound. According to some users it could have other disturbances such as a very long delirium-like trip and high anxiogenic potential, psychotic symptoms and psychomotor agitation [15] [26] [27].

## RELATED FATALITIES

BDF use might lead to death. Several fatalities possibly related to overdose of BDF are reported in Norway, Sweden and Denmark [14] [32] [34]. The EMCDDA reported at least 4 deaths related to BDF in these countries. In 2011, in the United States, two young adults died after overdosing on BDF, which they thought was 2C-E, and several others were hospitalized during the same incident [15] [37].

## YOU TUBE VIDEOS

The experimentation of BDF and its potency are well reported on the popular YouTube channel Neurosoup.
https://www.youtube.com/watch?v=c8MmMjvZ6uk#t=11
[38]

## GOOGLE TRENDS

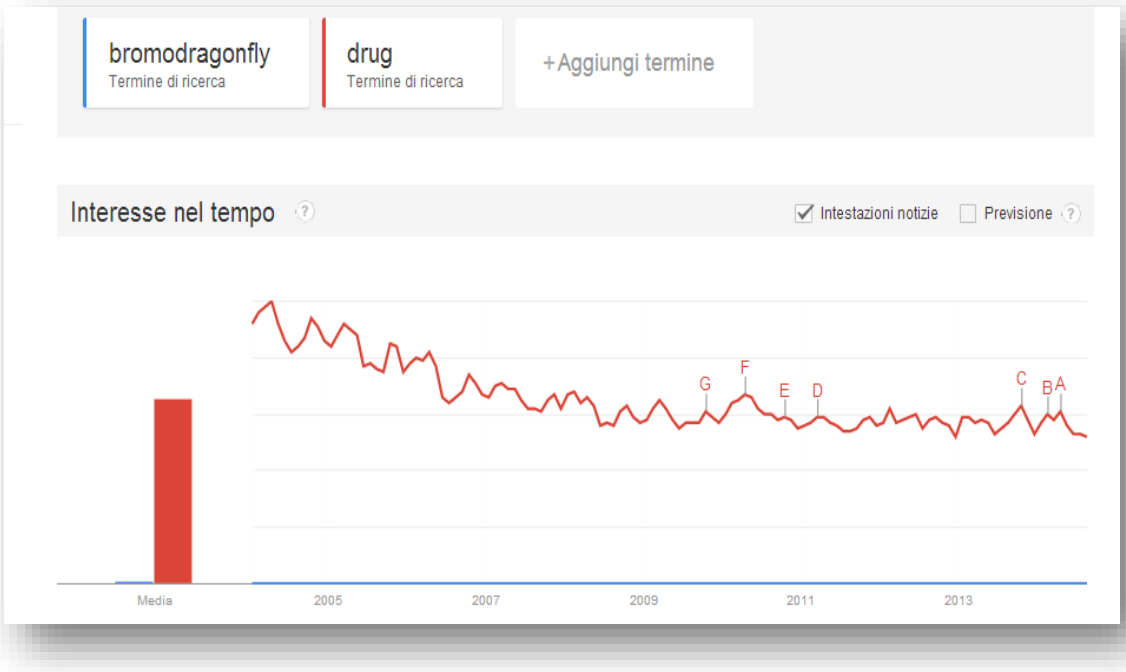



**Figure C: Google trends distribution of BDF.**

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# 25I-NBOMe

## *OVERVIEW*

Chemical name: 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine [1].

Synonyms: INBMeO; NBOMe-2C-I; 2C-INBOMe; BOM-CI; Cimbi-5; 25-I; Solaris; Smiles; N-Bomb; Wizard [2]

Active constituents: 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine

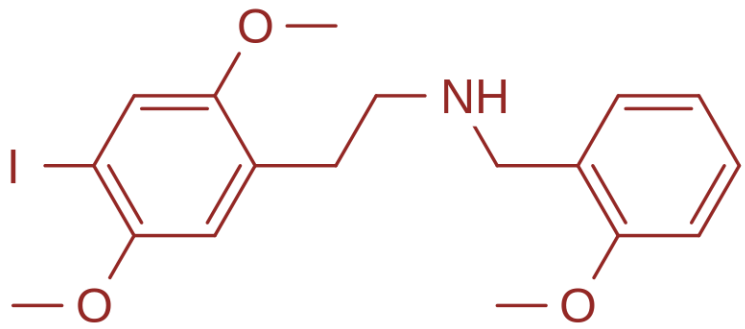


**Figure D: Chemical structure of 25I-NBOme**

Type: chemical

Origin: 25I-NBOMe is structurally a derivate of 2C-I and a substituted phenethylamine [3]. The first synthesis of this NPS was mentioned in a PhD thesis in 2003 by chemist Ralf Heim at the Free University of Berlin [4]; in 2008 the team of Professor D. Nichols investigated 25I-NBOMe and its properties at Purdue University (Indiana) [5] [6]. 25I-NBOMe contains the 2C-I substructure, substituted with a 'N-(2-methoxy)benzyl' group (Figure E).

Status: Novel

Chronology: 25I-NBOMe is novel a synthetic compound recently encountered on the designer drug market [3][7]. This NPS has nearly no history of human use prior to 2010 when it first became available online [2]. 25I-NBOMe belongs to the "NBOMe family": this name comes from the '**N-b**enzylmethoxy' substituent (-methoxy being written in chemical shorthand as '**OMe**'). In the last two years ten –NBOMe compounds have been notified to the EU early warning system [7].

## *KEY POINTS*

25I-NBOMe is a derivative of 2C-I (4-iodo-2,5-dimethoxyphenethylamine), a known synthetic derivative of phenethylamine with stimulant and hallucinogenic properties. 2C-I was the subject of a risk assessment at European level in 2003 [8] while more recently 25I-NBOMe has been associated with numerous non-fatal intoxications and some deaths, with seized material and use reported in many countries [3] [7] [9]; 25I-NBOMe is a potent full agonist of the serotonin 5-HT2A receptor and appears to have both stimulant and particularly powerful hallucinogenic effects.

## *CHEMICAL CHARACTERISTICS OF ACTIVE CONSTITUENTS*

IUPAC name: 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl]ethanamine
Molecular weight: 427.28 g/mol
Molecular formula: C18H22INO3
CAS Number: 919797-19-6
[7] [10]

## AVAILABLE INFORMATION ON PURCHASE PRICE

25I-NBOMe is potentially a highly profitable drug, since a relatively small amount of powder can generate many doses; in addition users may commonly mistake this substance for LSD. 25I-NBOMe is available online on websites where it is sold as a research chemical "not for human consumption". Its price is about 50 EUR for 50 mg powder [11] or about 15 EUR for three blotters (550 µg each) [12].

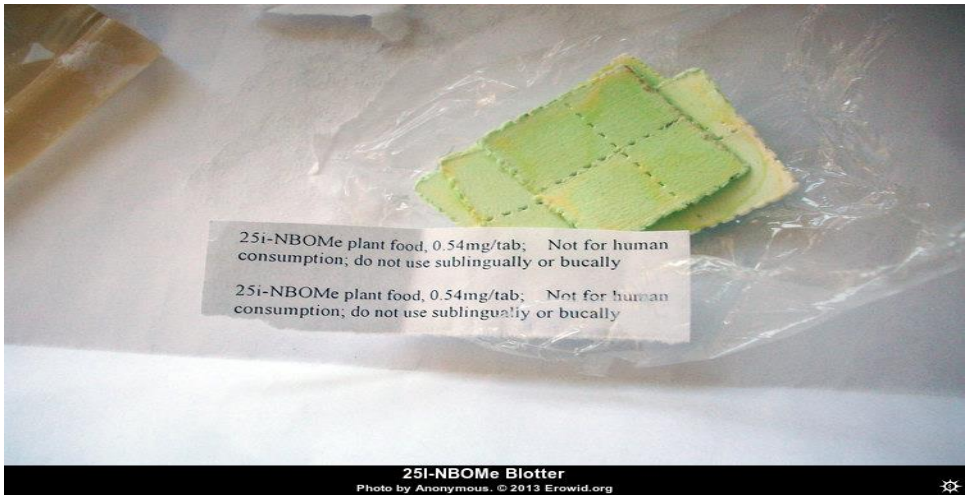


**Figure E Appearance of 25I-NBOME (Source: Erowid.com).**

## MODALITIES OF INTAKE:

25I-NBOMe is consumed in several modalities of intake. Online experience reported routes of administration including: sublingual/oral mucosae (especially using "blotter" paper), nasal (powder insufflation or absorption of liquid compound), oral. Some misusers also injected (intravenously and intramuscularly) or smoked 25I-NBOMe, while others consumed it even rectally [3] [13]. To be noted that 25I-NBOMe is widely rumoured in online forums to be orally inactive, however oral efficacy has not been disproven and apparent overdoses have occurred via oral intake. The more common modalities of intake include sublingual, buccal, and nasal/intranasal [14]. Similarly to LSD and other hallucinogenic substances (e.g. Bromo-dragonfly), 25I-NBOMe is often applied to sheets of blotter paper of which small portions (called *tabs*) are held in mouth to allow absorption through the oral mucosa [9]. There are reports of intravenous injection of 25I-NBOMe solution and other users smoked powdered form of this substance [15] [16]. An important observation is that 25I-NBOMe is active in sub-milligram doses: a common dose of the hydrochloride salt is 600–1.200 µg; the UK Advisory Council on the Misuse of Drugs states that a common dose of 25I-NBOMe is between 50 and 100 µg [9]. Other sources suggest that the threshold dosage for humans is 50–250 µg, with a light dose between 200–600 µg, a common dose at 500–800 µg, and a strong dose at 700–1500 µg [16]. This means that 25I-NBOMe has a significant risk of overdose: due to its level of potency, it is not possible to accurately measure a single dose without an analytical balance [3][6][9].

## LEGAL STATUS

In the US several NBOMe compounds have been temporarily scheduled in for 2 years with the possibility of an additional year. The temporary scheduling applies to 25C-NBOMe, 25B-NBOMe, and 25I-NBOMe [17] [18].
The UK Home Office announced that 25I-NBOMe would be made a class A drug in 10 June 2014 alongside

every other N-benzyl phenethylamine [19]. The NBOMe series of psychoactive substances became controlled in Israel in May 2013 [20]. Russia was the first country to have a specific law on the NBOME series (including 25I-NBOMe) becoming illegal in October 2011 [21]. Swedish Parliament added 25I-NBOMe to schedule I ("substances, plant materials and fungi which normally do not have medical use") in 2013 [22]. In February 2014 all the NBOMe series of psychoactive substances became controlled also in Brazil; Australia scheduled some products in 2012 [23] In 2011 Romania banned all new psychoactive substances, without class distinction [22]. In Italy 25I-NBOMe is not included in the banned scheduled substances [23].

## *CURRENT USE / MEDICINAL USE*

None.

## *INFORMATION ON RECREATIONAL USE/ MISUSE IN THE E.U. (OR ELSEWHERE)*

25I-NBOMe seems to be a popular NPS. Twenty-three EU Member States, US and Australia reported detections of 25I-NBOMe as a novel synthetic compound. It's important to highlight here that the "designed" chemical modification (the '*N*-(2- methoxy)benzyl' group) significantly enhances the potency of the phenethylamine structure: whilst a dose of 2C-I is around 20 milligrams, a dose of 25I-NBOMe is less than one milligram [26]. That means that at these levels of potency, attempting to use powder or liquid dosage forms is dangerous, with greater risk of overdose related to errors in 25I-NBOMe measurement. Some online suppliers have therefore chosen to sell it in the form of pre-loaded paper doses (blotters), similar to LSD tabs; so misusers can consume prepared dosage units [27]. Online experiences report 25I-NBOMe compound to be inactive if orally taken [13], so it is the most common modality of intake usually misuse by sub-lingual consumption or through insufflation. Some Internet suppliers claim to offer the materials to improve their bioavailability as a complex with hydroxypropyl- beta- cyclodextrin [9]. As a matter of fact there is no current human data to confirm or refute oral inactivity of 25I-NBOMe [3].

## *USE IN COMBINATION WITH OTHER COMPOUNDS*

According with online reports, 25I-NBOMe may be used on its own as well as in combination with other new psychoactive substances and/or controlled drugs [13] [28] [29], for example:

- Ketamine
-iMAO-A
-Cannabis
-MDMA
- Alcohol
- AMT
- DMT
- mushrooms

## *PHARMACOLOGICAL CHARACTERISTICS*

25I-NBOMe is a derivate of 2C-I, but it acts as a highly potent full agonist for the human 5-HTA receptor [30]

[31]. The addition to the 2-methoxybenzyl group in fact significantly enhances the affinity of 25I-NBOMe with a sixteen times potency *in vitro* than 2C-I itself [32]. 25I-NBOMe is one of the only full agonists of the human 5-HT2. Specifically an animal study described that 25I-NBOMe induces a dose dependent "head twitch behavioral response" (HTR) in mice, suggesting its psychedelic effects are precisely mediated by 5-HT2A. This study suggested that 25I-NBOMe is approximately 14-fold more potent than 2C-I *in-vivo* [33]. Stimulation of the 5-HT2A receptors appears in fact to be essential for the hallucinogenic effects of drugs such as LSD [34]. Although tested in animals, there are no reported human clinical trials.

## TOXICOLOGICAL EFFECTS

25I-NBOMe is the most commonly used substance of the NBOMe series, with 23 published cases of acute toxicity, additional 25 reports with similar effects reported directly to the EMCDDA and 8 fatalities related to its use [35]. According to the analysis of online information [36] effects usually last 6–10 hours if 25I-NBOMe is taken sublingually or buccally. When it is insufflated, effects usually last 4–6 hours or last significantly longer depending on dosage: for example durations longer than 12 hours have been reported at more high doses [36] [29]. 25I-NBOMe can also be vaporized and inhaled with quicker effects and shorter duration: this route of administration is however not recommended, unless using precise liquid measurement. As described in fact there are difficulties of measuring and handling substances like 25I-NBOMe, which are active in the microgram range. 25I-NBOMe has similar effects to LSD, though misusers report more negative effects while under this NPS influence and more risk of harm as compared to other more "classic" psychedelics [14].

Case reports of seven analytically confirmed 25I-NBOMe intoxicated British males who presented to an emergency room described the following potential adverse effects: tachycardia (n=7), hypertension (4), agitation (6), aggression, visual and auditory hallucinations (6), seizures (3), hyperpyrexia (3), clonus (2), elevated white cell count (2), elevated creatine kinase (7), metabolic acidosis (3), and acute kidney injury (1) [15].

There have been several reports of 25C-NBOMe and 25I-NBOMe misusers who experienced peripheral vasoconstriction and required medical attention. Some symptoms were: tingling, coldness, bluing, and numbness in the fingers, toes, lips, nose, and other extremities. Swelling in the hands, feet, and face have been reported. One user reported numbness lasting more than a week after use [36].

**Table II. 25I-NBOME - Medical and Psychopathological Effects**

| | |
|---|---|
| **Cardiac** | **Tachycardia; hypertension** |
| **Neurological** | **Seizures; clonus** |
| **Peripheral vascular** | **Vasoconstriction** |
| **Renal** | **Elevated creatine kinase** |
| **Other medical** | **Metabolic acidosis, hyperpyrexia, acute kidney injury** |
| **Psychoactive effects** | **Euphoria (dosage related); tachypsychia; visual distortions; synesthesia and chromesthesia; dissociation; anxiety; paranoia; confusion; agitation** |

## DESIRED PSYCHOACTIVE EFFECTS

25I-NBOMe is a recent NPS used as a hallucinogenic compound and a stimulant [2] [13] [29]. Users describe primary visual effects similar to LSD as for example strong open- and closed-eye visuals, including trails, color shifts and brightening. According to online experiences 25I-NBOMe has also more classical phenethylamine effects as: mood lift, euphoria, mental and physical stimulation, creative thinking, increased awareness, "appreciation" of music, life-changing spiritual experiences, "feelings of love and empathy", increased pattern recognition, including synesthesia and chromoesthesia [13].

Synthetically, "positive" effects reported are [3]:

- Strong open and closed eye visuals, including trails, colour shifts, brightening, etc.
- Mood lift
- Euphoria
- Mental and physical stimulation
- Increase in associative, creative thinking, increased awareness, appreciation of music, life-changing spiritual experiences
- Erotic, sexual thoughts and sensations
- Feelings of love and empathy

## PHYSICAL/ MEDICAL UNTOWARD EFFECTS

The intake of 25I-NMBOMe can also induce adverse reactions, both according to scientific literature and online experiences. When 25I-NBOMe is sublingually consumed, first effects are anecdotally described as particularly unpleasant with a metallic chemical taste along with a sense of numbness in the mouth; this effect can last up to an hour after the ingestion. This is a key difference between blotter papers containing LSD and those containing NBOMe drugs [37]. Furthermore according to online reports other physical untoward effects are for example [3][6]: pupil dilation, difficulty in focusing, unusual body sensations (facial flushing, chills, goose bumps), slight increase in heart rate, yawning, nausea. Differing from other phenethylamine compounds 25I-NBOMe seems not to act as an appetite suppressors. Particularly relevant among medical effect of 25I-NBOMe is vasoconstriction [36].
Moreover, summarising available scientific literature, especially published case reports, 25I-NBOMe misuse lead to severe medical untoward effects and symptoms at several levels [15 [38] [39] [40] [41] [42]:

- Cardiovascular (hypertension and tachycardia)
- Neurological (seizures and clonus)
- General and metabolic (elevated creatine kinase [39] hyperpyrexia, metabolic acidosis, rhabdomyolysis [43])
- Renal (acute kidney failure)
- Multi Organ Failure [44] [45] [46]
- Cerebral edema [43]

## PSYCHOPATHOLOGICAL DISTURBANCES ASSOCIATED WITH ITS USE

25I-NBOMe is a powerful hallucinogenic phenethylamine, which might cause psychopathological consequences, generally more common as the dosage increases [3][13]:

- General change in consciousness
- Difficulty focusing
- Change in perception of time and time dilation
- Confusion
- Insomnia
- Looping, recursive, out of control thinking
- Paranoia, fear, and panic
- Unwanted and overwhelming feelings
- Unwanted life-changing spiritual experiences.

Furthermore, 25CNBOMe is able to cause a wide range of hallucinatory states, including visual and auditory hallucinations [12].

## RELATED FATALITIES

25I-NBOMe deadly intoxications have been reported by Australia (at least 2 deaths), Belgium (1 unconfirmed death), Poland (1 unconfirmed death), the United Kingdom (1 death) and the USA (5 deaths). Many but not all of these cases have been analytically confirmed [3].

25I-NBOMe misuse had also an important media coverage: for example in May 2013, this compound has reportedly led to five overdose deaths in the United States as documented by media [46]; in June 2012, two teens in Grand Folk, North Dakota and East Grand Forks, Minnesota fatally overdosed on a substance that was allegedly 25I-NBOMe [47]; a 21-year-old man from Little Rock, Arkansas died in October 2012 after taking a liquid drop of the drug nasally at a music festival [48]; in January 2013, a 18 year-old in Scottsdale, Arizona, died after consuming 25I-NBOMe sold as LSD; a toxicology screening found no other drugs in the person's system; 25I-NMBOMe is the suspected cause of death in another Scottsdale, Arizona, incident in April 2013 [9]; and from May 2013 to May 2014, 25I-NBOMe caused other four teenage deaths in the US [49]. 25I-NBOMe has been implicated in multiple deaths also in Australia [8]: in March 2012, a man in Australia died from injuries sustained by running into trees and power poles while intoxicated by 25I-NBOMe [50] and on June 5 2013, a Sydney teenager died jumping off a balcony thinking he could fly, under the effects of this compound [51] [52].

Therefore recent literature and occurred events describes 25I-NBOMe as a potential deadly compound [52] [53] [54] [55] [56] [57], because a) untoward medical effects and b) altered state of consciousness; a recent case report also confirmed the emergence of 25I-NBOMe as an LSD substituted with potentially lethal consequences [58].

## YOU TUBE VIDEOS

25I-NBOMe is popular also in YouTube videos, for example in the famous NeuroSoup channel:

- NeuroSoup "NBOMe Research Chemicals" www.youtube.com/watch?v=5CqrRoaBaag [59]
- NeuroSoup "LSD vs 25I-NBOMe" www.youtube.com/watch?v=kJ6hGs4fRmA [60]
- NeuroSoup "Evaluating the Safety of 25I-NBOMe" www.youtube.com/watch?v=RI9Q0oB8yuo [61]

## GOOGLE TRENDS

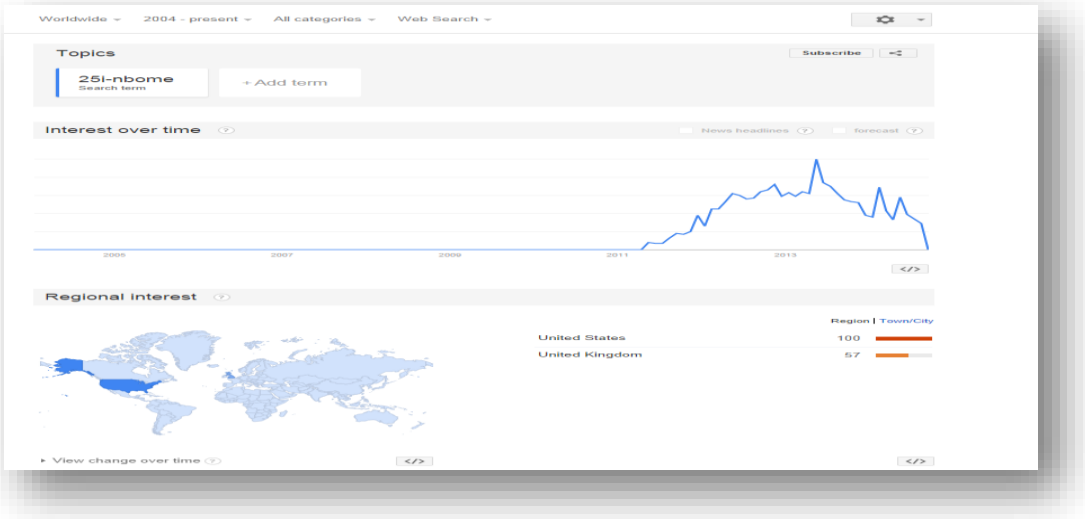


**Figure F: Distribution of 25I-NBOMe on Google Trends.**

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# Kratom (Mitragyna Speciosa)

## *OVERVIEW*

Botanical classification [1][2]:

- familia: Rubiacieae
- genus: Mitragyna
- specie: M. speciosa

Synonyms: Kratom; Ketum; Kakuam; Ithang; Thom; Mambog; Kripton [2].

Active constituents: Kratom properties are related to specific active molecules of the plant; in fact of the over 40 alkaloids isolated, the most abundant are mitragynine (66.2% based on the crude base of the plant) and other analogues (speciogyne, paynantheine and speciociliatine) [3] [4]. In addition, a new alkaloid, 7 Hydoxymitragyne has been isolated as a minor constituent (2%) [5][6][7]. Mitragynine and 7-Hydroxymitragyne are considered the most effective active constituents of Kratom.

Type: botanical, ethno drug.

Origin: M. Speciosa is a tropical tree indigenous to Southeast Asia and Africa (especially Thailand, Indonesia and Papua New Guinea); in these regions its leaves are traditionally used as medicinal remedies and stimulants [8]. M. speciosa trees grow primarily in tropical regions with normal height of 4-9 m, but certain plants can reach 15-30 m. The leaves are of a dark, glossy green, measuring over 18 cm long and 10 cm wide with an ovate/acuminate shape (see Figure G). The plant yields yellow flowers, growing in clusters attached to the leaf axil on long stalks, bearing up to 120 flowers each. The seeds are winged [7][9][10]. The leaves fall abundantly during the dry season of the year and new growth is produced during the rainy season [11]. Since immemorial time Kratom has long been used as a herbal drug in these regions [12]. Kratom was used in Thailand and Malaysia by manual labourers to enhance productivity due to its euphoric effect at low doses ("coca-like" stimulation) [12] [13]. At higher doses Kratom has also an opioid-like effect: its use to treat pain and opium withdrawal was described as early as the nineteenth century [14]. The use of Kratom was historically associated with working class men, while its use by women was considered unusual [15].

Chronology: mitragynine was isolated first by Field in 1921; its chemical structure was clarified in 1963-1964 while more recently 7-hydroxymitragynine was identified in the leaves (1994) [16]. Despite its long history and widespread use in South East Asia, Kratom has only recently begun to receive attention as a NPS ethno drug in Europe as well as the US [17] [18] [19]. Anecdotal reports on Kratom subjective experiences on the Internet have been recorded since 2001 [19]. Moreover, the Drug Enforcement Administration (DEA) began its warnings about this substance as early as 2005 [21].

## *KEY POINTS*

Mitragyna speciosa is a leafy tree growing from 3-20 meters tall in Thailand and South-East Asia; its leaves contain several alkaloids, including mitragynine and 7-Hydroxymitragynine. Chewing leaves, drinking Kratom tea or juices are the traditional ways of intake of this ethno-drug with the aim of obtaining both stimulant and opioid effect. Recently Kratom has appeared in online European and US market as a novel psychoactive substance, in form of leaves, powder or pills [2].

Figure G: Leaves of Kratom, and online Kratom products.

## CHEMICAL CHARACTERISTICS OF ACTIVE CONSTITUENTS

Mitragynine is the most abundant alkaloid in the leaves. It was first isolated in 1921 and its chemical structure was fully elucidated in 1964.

IUPAC name: (αE,2S,3S,12bS)-3-ethyl-1,2,3,4,6,7,12,12b-octahydro-8-methoxy-α-(methoxymethylene)-indolo[2,3-a]quinolizine-2-acetic acid methyl ester
Molecular weight: 398.50 g/mol
Molecular formula: C23H30N2O4
CAS Number: 4098-40-2

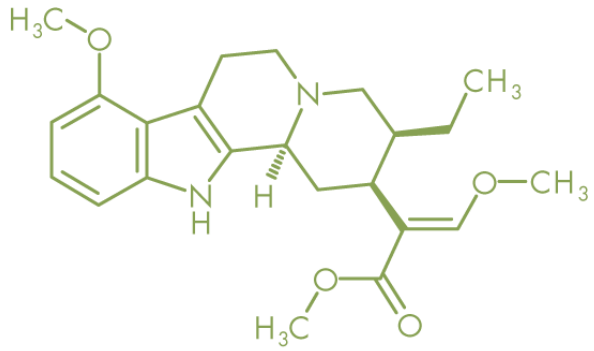


Figure H: Chemical structure of Mitragynine.

7-Hydroxymitragynine is present only in very small amounts in Kratom leaves and was identified in 1993.

IUPAC name: (αE,2S,3S,7aS,12bS)-3-ethyl-1,2,3,4,6,7,7a,12b-octahydro-7a-hydroxy-8-methoxy-α-(methoxymethylene)-indolo[2,3-a]quinolizine-2-acetic acid methyl ester
Molecular weight: 414.50 g/mol
Molecular formula: C23H30N2O5
CAS Number: 174418-82-7
[21]

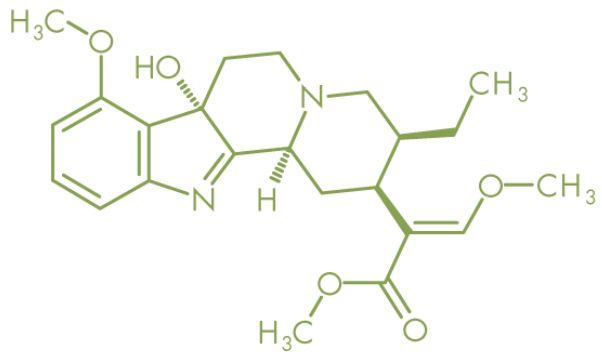

**Figure I: Chemical structure of 7-Hydroxymitragynine.**

## *AVAILABLE INFORMATION ON PURCHASE PRICE*

Kratom is considered a novel ethno-drug, a compound used by traditional societies and newly misused in Western countries. Kratom products in fact are available in the online market and prices vary between countries, depending on the type and amount of the purchased product. For example according to the EMCDDA Internet surveys conducted in 2008, the prices of 'Kratom 15X' extracts ranged from EUR 2 to 10 per gram in the sampled European countries. In 2011, a follow-up EMCDDA snapshot of 314 online shops found that prices ranged from EUR 6 to 15 per 10 gram of dried Kratom and EUR 7 to 8 per gram of 'Kratom 15X' extract [22]. During our last research on the web, prices were even lower (from less than 1 Euros per gram for Kratom power) [23] [24] [25].

## *MODALITIES OF INTAKE:*

Traditionally M. speciosa can be consumed by chewing leaves, ingesting or drinking the extract and less often by smoking them. In Thailand, Kratom leaves are often chewed fresh (usually after removing the stringy central vein). Dried leaves can also be chewed, but since they are a bit tough, most people prefer to crush them up (obtaining a powder) in order to be swallowed. This powdered Kratom form can also be mixed with fruit juice to mask the taste. Furthermore, lemon juice can also be added to facilitate the extraction of plant alkaloid [18]. Dried Kratom leaves are often made into a tea and then drunk (this is the most frequently used method in the West) [12][25]. Kratom can be smoked, but without the advantage over chewing or making a tea: the amount of leaf that constitutes a typical dose is too much to be smoked easily. A paste-like extract can be prepared by lengthy boiling of fresh or dried leaves; this produced syrup can be mixed with finely chopped leaves of the palm tree, made into pills and smoked in bamboo pipes ("madatin") [26]. Small pellets of this extract can be ingested, or again the compound can be dissolved in hot water and consumed alone or mixed with other ordinary herbal tea to make it more palatable [27]. Fora users suggest similar methods of consumption for online products, including the so called "toss and wash" way, that means to put some powdered Kratom into mouth and swallow it with water or other beverage [28]. Other people use to consume it with food, mixing it with yoghurt or preparing cookies in order to contrast the bitterness of the compound. Finally others prefer to add it to some alcoholic beverage [29] [30]. A particular method popular in Southern Thailand is the cocktail called "4x100". The origin of the name is unclear, probably related to its four ingredients: Kratom leaves + codeine/diphenhydramine cough syrup + cola and a fourth variable component (including simple ice, antidepressants, or other illicit substances). This preparation seems to mimic alcohol effects (for this reason 4x100 formula is popular among Muslim youthful) and also to increase aggressiveness (for this reason it is reported as a stimulant in Thai militaries) [31] [32].

## LEGAL STATUS

Kratom has different legal status in different countries.
Mitragyna speciosa is an uncontrolled plant in the United States. This means all parts of the plant and its extracts are legal to cultivate, buy, possess, and distribute without a license or prescription; when sold as a supplement, sales must conform to U.S. supplement laws [33]. Recently, in February 2014, the FDA issued "Import Alert 54-15" that seems to provide customs and border agents broad authority to seize Kratom products from a number of suppliers outside the US. Indiana, Iowa, Louisiana, Massachusetts included Kratom in the controlled substances list [34].
In Europe Mitragyna speciosa and/or mitragynine and/or 7-hydroxymitragynine are currently controlled in a number of Member States such as Denmark, Latvia, Lithuania, Poland, Romania and Sweden [22]. In Italy this compound is not included in the banned scheduled substances [33] [35].
Possession of Kratom leaves is illegal in Thailand, despite the tree being native to the country. The Thai government passed the *Kratom Act 2486* which went into effect on August 3, 1943. This law made planting the tree illegal and requires existing trees to be cut down. This law was not found effective, since the tree is indigenous to the country. A large aspect of Thai culture supports Kratom, however the Thai government had initiated a program of destroying Kratom trees by burning forests. Eradication campaigns often destroy not only trees but also other trees and wildlife in these areas, which are often, untouched rainforests. A general consensus exists in southern Thailand, where the use of Kratom is endemic, that Kratom use and dependence causes little, if any, health risks [31]. More recently in 2013 the Justice Ministry of Thailand suggested removal of Kratom from the narcotic drug list relating to Category 5 of the Narcotic Drug Law of 1979, though still recommended regulating Kratom in other ways due to its effects on the nervous system [36]. The use of Kratom leaves (locally known as 'ketum' which roughly translates as 'Goblin') is prohibited in Malaysia under Section 30 (3) Poisons Act 1952 and the user may be penalized with a maximum compound of MYR 10,000 (USD 3,150) or up to 4 years imprisonment [37]. Certain parties have urged the government to penalize the use of Kratom under the Dangerous Drugs Act instead of the Poisons Act, which will carry heavier penalties [38].

## CURRENT USE / MEDICINAL USE

Kratom has a tradition as a herbal drug: in Malaysia and Thailand the leaves are used to treat intestinal infections, muscle pain, to reduce coughing and diarrhoea [15][39]. M. Speciosa preparation had been used by Mali and Thai natives for its coca and opium-like effects to enhance tolerance for hard work under the hot sun [13][15][31], and then, in the nineteenth century, as an opium substitute in treatment of opium addiction [31].
Tradition and ethno-medicine suggest that M. Speciosa may have several properties (including analgesic, antipyretic, euphoric, anti-depressant and anxiolytic effects) supposing to act also as an immune booster, anti-viral agent, diabetes- and appetite- suppressing drug [11] [40].
On the contrary in modern medicine there is not approved use of Kratom or its alkaloids.
In the Western societies Kratom is considered a novel substance with recreational and self-medication purposes: plant preparations are easily accessible from local coffee shops and web based “legal-highs” pharmacies [41] [42] inducing patients to use the plant as a self-treatment, for example in modulating opiate and alcohol withdrawal, or chronic pain [41]. Kratom is marketed as a cheaper alternative to the established opioid replacement therapies and is obtainable without medical prescription [18]. Anyway it has been suggested that the therapeutic potential of Kratom (and its active constituents) should be explored for the treatment of pain, depression and drug withdrawal symptoms [22].

## INFORMATION ON RECREATIONAL USE/ MISUSE IN THE E.U. (OR ELSEWHERE)

In recent years Kratom has become popular in Europe, US and other countries (e.g. Japan) as a recreational novel compound [21] [22] [43]; it has been sold for its narcotic effects around the world, mainly via Internet vendors. The recreational potential seems to be related to its stimulant properties and an opioids-like effect,

affecting Mu and Delta opioid receptors. Online users report describes tolerance (requiring more product to achieve the same effects) and also a cross-tolerance (meaning that a Kratom user can build tolerance for both Kratom and opiates). This could pose a problem for doctors prescribing pain medication to someone after regular Kratom use [44]. Another reason of concern is the action of other isolated compounds (peciociliatine, speciogynine and paynatheine) whose effects were not inhibited by naloxone in animal studies [45] [46].

## USE IN COMBINATION WITH OTHER COMPOUNDS

Kratom can be used in combination with other substances, for example [47]:
- Cannabis
- Methadone
- 2C-E
- Benzodiazepines
- Kava
- Alcohol
-Mephedrone
- Salvia Divinorum
-Mushrooms
- 4-HO-MiPT

Online guide anyway suggest not consuming Kratom with other sedative drugs (alcohol, benzodiazepines or opioids), stimulants (cocaine or amphetamine) or iMAO (including natural anti-depressants like Peganum harmala) [27].

## PHARMACOLOGICAL CHARACTERISTICS

Mitragynine is an indole alkaloid, structurally similar to yohimbine and with an *in-vitro* activity at both supraspinal opioid mu- and delta- receptors [48]. The mu- receptor mediates analgesia, euphoria, and respiratory depression, which explain the mitragynine analgesic effect, as well as its amelioration of opiate withdrawal symptoms. Mitragynine has also been postulated to be involved in the activation of descending noradrenergic and serotonergic pathways in the spinal cord [49] and other animal studies suggest that mitragynine may stimulate post-synaptic alpha-2 adrenergic receptors and/or block stimulation of 5-HT2A receptors [50]. However, there are no reports of mitragynine being screened for affinity at these specific receptors. The chemical similarity between the Kratom alkaloids and other biologically active compounds suggests that they may be involved in activation or inhibition of other receptor systems. Additional alkaloids isolated from Kratom, including 7-hydroxymitragynine, possess anti-nociceptive effects in animal models and a high affinity for opioid receptors [50]. Studies on 7-hydroxymitragynine have also demonstrated that this alkaloid may be more potent than morphine, even after oral administration [51], with a better oral bioavailability and blood brain barrier penetration than mitragynine [8] [45]. Recent findings seem also to confirm a Kratom anti-inflammatory activity [52] [53].

## TOXICOLOGICAL EFFECTS

Kratom is consumed as a sort of “legal opioid” with an unusual combination of stimulant and opioid –like effects [17]. Consumption of Kratom can lead to anorexia, dry mouth, problems in diuresis and constipation after long-term use at high doses [15]. While traditionally there is few evidence of a dosage increment among long term users, withdrawal symptoms are well reported: these symptom range includie hostility, aggression, aching of muscles and bones, jerky movements of the limbs, anorexia / weight loss and insomnia [15]. Long term consumption can also cause darker skin due to the capacity of mitragynine to increase the production of a melanocytes-stimulating substance [13] [15]. Of particular concern, there have been several reports of seizures occurring in individuals who have used high doses of Kratom, either alone or in combination with other drugs, such as modafinil [41] [54] [55]. Recent studies also described hepatic toxicity in chronic users of Kratom [56]

[57]. It is not irrelevant to note that in clinical cases the use of Kratom is often associated with the consumption of other substances such as medications, other illicit drugs or herbal products [17].

## DESIRED PSYCHOACTIVE EFFECTS

According to online reports and traditional experiences subjective effects of Kratom depend on the dosage: at low to moderate dose (1-5 g) has a mild pleasant stimulant effect while at moderate-high dose (5-15 g) the compound has opioid-like analgesia and sedation [27] [58]. Users report that, at low stimulant level mind is "more alert", physical energy and sometimes sexual arousal are increased, ability to do physical work may be improved and they also described entactogenic effects like empathy and euphoria. Some people find this level edgy rather than pleasant [20] [58]. At a higher level, which is more sedative and analgesic, users refer to be less sensitive to physical or emotional pain, to feel and look calm, to have a general feeling of comfortable pleasure [27]. Other reports an increase of empathy feelings [58].

| Table III. Positive effects of Kratom (Source: Erowid.org) |
|---|
| **Simultaneous stimulation and sedation** |
| **Feelings of empathy** |
| **Feelings of euphoria** |
| **Aphrodisiac qualities for some people** |
| **Vivid waking dreams** |
| **Useful with physical labour** |
| **Low doses can result in a lasting "glow" in some people, feeling better than normal the next day** |
| **Increases sociability and talkativeness** |

## PHYSICAL/ MEDICAL UNTOWARD EFFECTS

The consumption of Kratom does have possible side effects such as nausea, constipation, sleep problems, temporary erectile dysfunction [44], itching and sweating [19] but also hyperpigmentation, tremor, anorexia and weight loss in long term addiction [15]. Some users describe hair loss, probably related to the daily use of Kratom [59]. Reported withdrawal symptoms may include muscle aches, irritability, crying, runny nose, diarrhoea, and muscle jerking [27]. A recent study described a case of Adult Respiratory Distress Syndrome after ingestion of Kratom [60] and another case suggested Kratom to induce hypothyroidism [61].

| Table IV. Negative effects of Kratom (Source: Erowid.org) |
|---|
| **Very bitter taste** |
| **Dizziness, nausea and/or vomiting at higher doses** |
| **Mild depression during and/or after** |
| **Increase in (perceived) body temperature (feel hot and sweaty)** |
| **Hangover similar to alcohol, including headaches and sometimes nausea (at higher doses)** |
| **Desire to repeat experience more frequently than intended, can lead to addiction** |
| **Tolerance building quickly after a few days in a row of repeated use, tolerance to effects reduces with a one to three days of abstinence** |

## PSYCHOPATHOLOGICAL DISTURBANCES ASSOCIATED WITH ITS USE

Kratom and its several alkaloids are poorly understood in their action on opioid receptors [62] [63], but online information and literature agree to consider this ethno-drug able to cause abuse, dependence and addiction [3] [19] [20] [22] [60] [64]. Some evidence suggested protocols in order to manage the detoxification from Kratom, for example using dyhydrocodeine and lofexidine [65], but more studies are needed. Sunwanlert (1975) reported that chronic exposure to M. Speciosa could be followed by withdrawal symptoms in humans, that may include hostility and aggression [15] and in other cases due to M. Speciosa abuse psychotic symptoms can occur [61]. Little evidence can be described about the use of Kratom as self-medication [66] even if this practice seems common [20]. A recent study suggested that Kratom can also impair cognitive functions [67].

## RELATED FATALITIES

Literature strongly suggests that Kratom is also a deadly substance, especially when mixed with other compounds. For example there are case reports of deaths resulted from the use of a Kratom-based product known as "Krypton" [68], online touted as a very potent form of M. Speciosa and marketed in Sweden. During the past years, there have been reports of 9 deaths related to the use of Krypton. In a case series, subsequent forensic studies revealed that Krypton contained high amounts of the exogenous pharmaceutical agent *O*-desmethyltramadol (metabolite of tramadole), which has opioid and neuromodulator activity, and it had been added to the plant material. Even though mitragynine was also detected in the products, it was not determined how the two substances may have interacted to cause death. The presence of this contaminant in online products is well documented [69] [70].
Other "deadly cases" are available: an article [71] described a fatal reaction that appeared to be associated with a mix with propylhexedrine (an α agonist and amphetamine-like stimulant, used as decongestant inhalers); another case indicated Kratom responsible for the death of a 17-year-old boy [72]; a post-mortem detection of Kratom was screened in a 24-years man found unresponsive in bed [73].

## YOU TUBE VIDEOS

The experience with Kratom was described by Neurosoup YouTube Channel.
www.youtube.com/watch?v=QLnl4WAAm7Q [74]

Other videos describe Kratom and its effects [75] [76] [77]:
Kratom Effects www.youtube.com/watch?v=72QT-2HTwGo
Kratom: uses, types and properties. www.youtube.com/watch?v=OWIP1hS0ZQ4
Kratom Documentary: interview with Kratom users. www.youtube.com/watch?v=KaZqXw_zTNE

## GOOGLE TRENDS

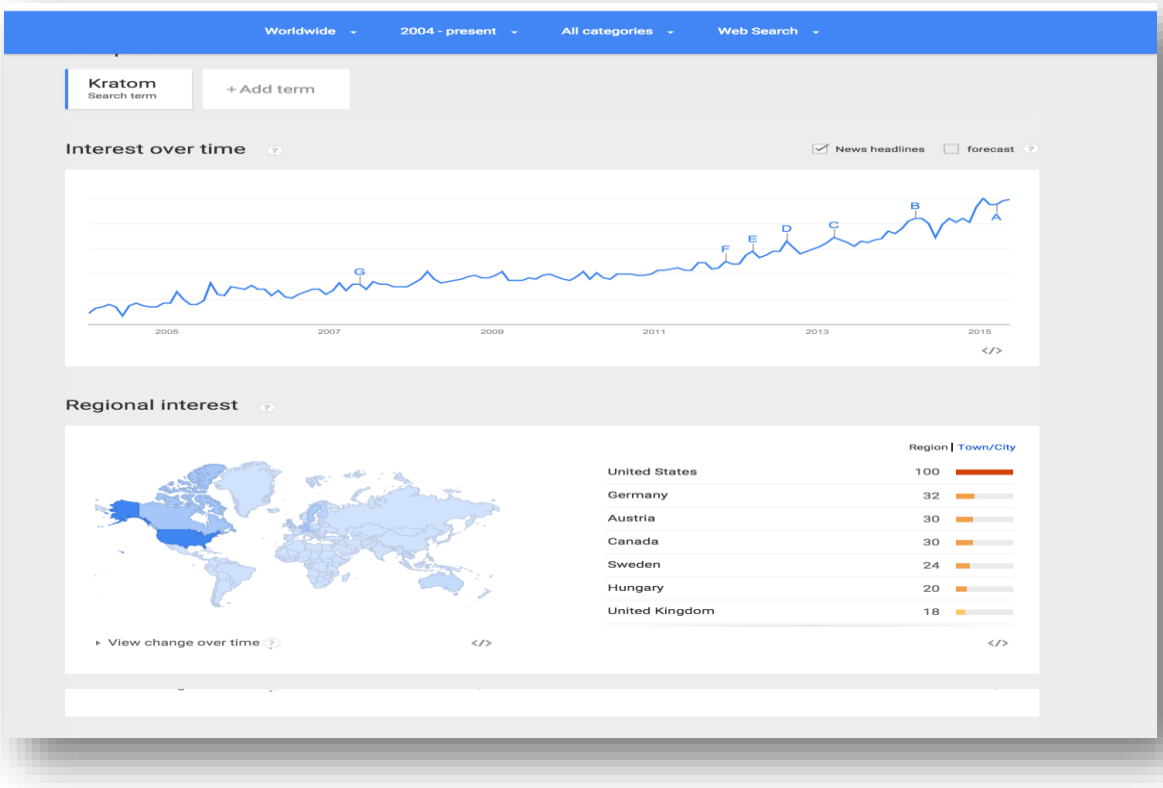


**Figure J: Kratom on Google Trend.**

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# Alfa- PVP

## *OVERVIEW*

Chemical name: α-Pyrrolidinopentiophenone [1] [2].

Synonyms: alpha-pyrrolidinovalerophenone; α-PVP; alpha-PVP; O-2387; β-ketone-prolintane; Prolintanone; "gravel" [3] [4].

Active constituents: (*RS*)-1-phenyl-2-(1-pyrrolidinyl)-1-pentanone [5]

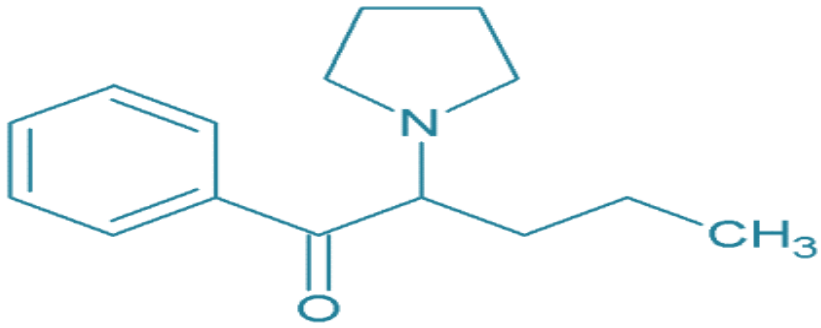


**Figure K: Chemical structure of Alpha-PVP**

Type: chemical

Origin: Alpha-PVP could be considered a substance analogue of MDPV (3,4-methylene- dioxypyrovalerone), belonging to synthetic cathinones group [1][3][6]. It was first synthetized in 1960s but became popular recently as a recreational synthetic psychoactive substance [3][7][8].

Status: Novel

Chronology: Alpha –PVP was developed in 1960s as a synthetic derivate in the cathinones family but it has been recently (2013) related to three deaths [7] dramatically confirming its presence on the online market [9][10] [11] [12]. It was also involved in a case of impaired driving case [13]. No first – hand accounts of effects in peer reviewed literature.

## *KEY POINTS*

Alpha – PVP is a Novel Psychoactive Substance with an arising popularity (see for example Google Trends results); it acts as a stimulant (its structure is similar to amphetamine and cathinones) [14] with an unknown neurotoxicity. Due to its similarity to MPDV this compound seems to be as norepinephrine-dopamine reuptake inhibitor (NDRI) [15] [16].

## CHEMICAL CHARACTERISTICS OF ACTIVE CONSTITUENTS

IUPAC name: (RS)-1-phenyl-2-(1-pyrrolidinyl)-1-pentanone
Molecular weight: 231.333 g/mol
Molecular formula: C15H21NO

## AVAILABLE INFORMATION ON PURCHASE PRICE

Alpha –PVP is sold online in form of white crystal or also in a blue variant form [17] [18]. The price online is USD 1-6 / gram [19] [20]; it is sold through international websites and laboratories based mostly in China. Sites on the online market deliver the product for 16.5 Euros/ gram with a discount in case of high dosage orders [20].


**Figure L: Appearance of Alpha-PVP.**

## MODALITIES OF INTAKE:

Alpha-PVP in crystal form can be ingested, sublingually administrated, smoked, insufflated, vaporized [21] or even injected with severe health risks [22]. According to online reports most common modalities of intake seem to be insufflation and smoking [23]. Online fora suggest very low dosage at first time (0.1-0.2mg/kg) even to avoid allergic reaction, reaching 10-50 milligrams per dose [24] [25]. The average insufflated/smoked dosage is considered 25 mg [26] [27] but users describe a powerful stimulant effect also at a lower dosage. Some online experiences and clinical cases describe abuse of alpha-PVP at higher dosage.

## LEGAL STATUS

Alpha - PVP is a Schedule I drug in few counties: New Mexico, Delaware, Oklahoma, and Virginia [3]. On January 28, 2014, the Drug Enforcement Administration listed it, along with 9 other synthetic cathinones, on the Schedule 1 with a temporary ban, effective February 27, 2014 [26]. As a matter of fact the DEA presented analytical data to assist forensic laboratories that encounter α-pyrrolidinopentiophenone in casework [5].
Alpha – PVP is also illegal in New South Wales after two deaths [10].

## CURRENT USE / MEDICINAL USE

None.

## INFORMATION ON RECREATIONAL USE/ MISUSE IN THE E.U. (OR ELSEWHERE)

Online reports declare analogies with stimulants like cocaine, amphetamines and other synthetic cathinones (like MDPV). Users suggest a very low dosage of the compound, particularly during the first consumption [23] [24]. Alpha – PVP effects have been described in several online fora: it is discussed mainly in English websites, but also in Italian [25], Spanish [27], and other European countries [28]. Similarly to other NPS, online sellers seem to be able to send the product anonymously and internationally [29] [30] [31].

## USE IN COMBINATION WITH OTHER COMPOUNDS

Alpha-PVP seem to be a powerful stimulant itself; few users suggest a combination with:

- Energy drinks [23]
- Lidocaine
- Percocet (oxycodone), Baclofen, pyrazolam, visteril, cannabis, olanzapine, theanine: such compounds suggested to support comedown phase by some psychonauts. Some users noted that THC could increase psychotic symptoms [32].
- Kratom: for managing the comedown [32]
- Lyrica: for managing the comedown [33]

## PHARMACOLOGICAL CHARACTERISTICS

Alpha – PVP is a CNS stimulant chemically related to pyrovalerones (e.g. MDPV) [34]. A recent study [16] investigated the effects of this compound on mice CNS comparing it with that of methamphetamine: authors described an earlier and stronger locomotor activity, a rapid and shorter increase of dopamine in the striatum (D1 and D2 receptors). This data suggests an activity as monoamine uptake receptors [1] but with a unique (and unknown) pharmacological profile.

## TOXICOLOGICAL EFFECTS

Alpha –PVP toxicological effects on human are unknown. Data available on mice suggests similar properties to other compounds (methamphetamine and synthetic cathinones): alpha – PVP acts as a dopamine(DA) releasing agent, which is reasonably the main mechanism responsible of its CNS stimulation and psychopathological consequences.
Online experiences describe (with 10-25 mg as average dosage through insufflation/smoking) [21] [23] [24]

[35] [36]

- 2-5 minutes after the intake: a mild euphoric effect
- 20-40 minutes: euphoria and sexual stimulation
- 1 hour: peak of stimulant effect
- 2 hour: decreased effects
- 3 hour: come down

**Table I – Alpha –PVP : Medical and Psychopathological Effects**

| | |
|---|---|
| **Cardiac** | **Tachycardia; hypertension** |
| **Neurological** | **Sexual arousal** |
| **Peripheral vascular** | **Vasoconstriction – sweating** |
| **Other medical** | **Unknown** |
| **Psychoactive effects** | **Euphoria, alertness, tachypsychia;**<br>**- Especially at high dosage: auditory and visual distortions/hallucinations (Ekbom's syndrome); dissociation; anxiety; confusion; agitation, paranoia** |

## *DESIRED PSYCHOACTIVE EFFECTS*

According to online experiences reported by users [21] [23] [24] [35] [36], alpha –PVP is suggested as an alternative to amphetamines, coke, methamphetamines, methylphenidate due to its stimulant properties. Specifically this compound can induce:

- Euphoria (in 15 seconds, with maximum effect in 1 hour, lasting for 3- 4 hours; 20 mg) [35] [37]
- Sexual arousal: reported in many experiences as an important effect [35] [36]; this effect is in common with 2C-B, 4-FA, 4- DMAR [38]
- Tachypsychia [21] [23]
- Alertness [21] [23]

## *PHYSICAL/ MEDICAL UNTOWARD EFFECTS*

Alpha – PVP seems to be similar to other stimulants also in the main side effects:

- Tachycardia: described as an important untoward and unpleasant effect, especially when insufflated [39];
- Sweating and vasoconstriction [40];
- Throat, chest and lung pain (especially when vaporized) [41];
- Loss sensibility on tongue (sublingually administration) [21];
- Unpleasant taste;
- Jaws clenched;
- Vomit (high dosage) [23];
- Kidney pain (when mixed with magnesium sulphate) [24].

## PSYCHOPATHOLOGICAL DISTURBANCES ASSOCIATED WITH ITS USE

Several online records suggest a high psychopathological risk as consequence of alpha- PVP use, such as:

- Anxiety and panic attack [33];
- Insomnia (almost for 8 hours with single dosage) [41];
- Paranoia, delusions and hallucinations: both auditory and visual hallucinations reported with high dosage (1200 mg, re-dosing the compound in a single night) in the form of delusional parasitosis [42];
- Compulsion to re-dose: reported by many users [21] [23] [35] [36];
- Depressive feelings (comedown) [32];
- Alpha- PVP has been found in a case of aggressive behavior [7].

## RELATED FATALITIES

Presence of alpha- PVP has been reported in suicides and polydrugs overdoses [43] while the drug was found to be cause or a significant cause in three deaths [7] with concentrations of 0.1, 0.5 and 0.29mg/L.

## YOU TUBE VIDEOS

YouTube A-PVP review: https://www.youtube.com/watch?v=DcJqu70hSbc
YouTube A-PVP review update: https://www.youtube.com/watch?v=JZlMRKg8_H8

## GOOGLE TRENDS

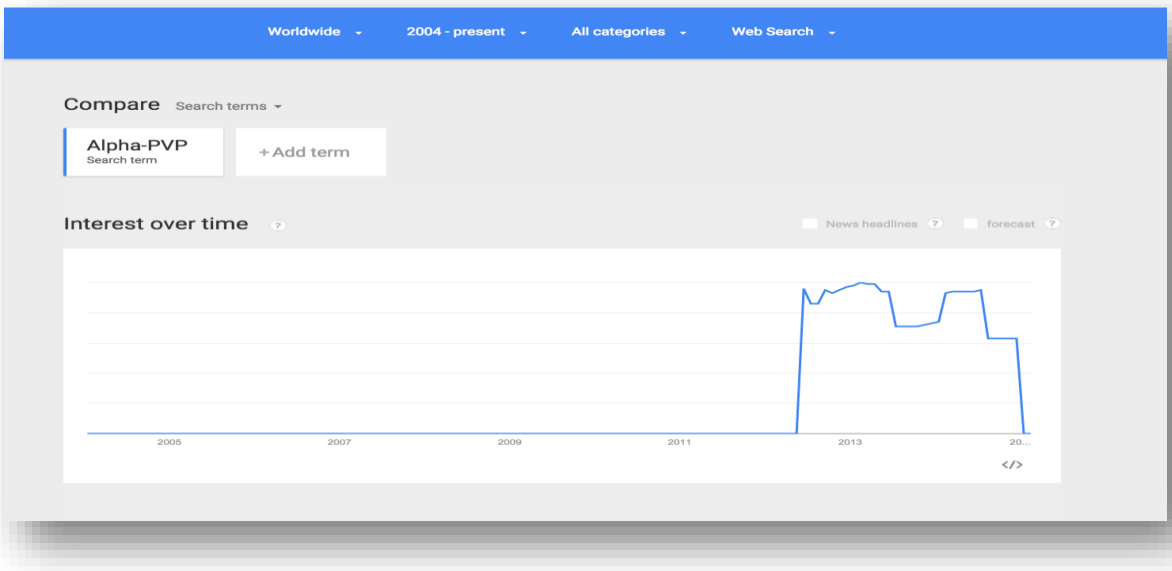


**Figure M: Worldwide distribution of Alpha-PVP on Google trends.**

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# CASE REPORTS

**Case report n. 1: "*Alice in wonderland*"**

This case report was collected in the Dual Diagnosis Unit of the Italian Clinic "Parco dei Tigli", located in Padova in the North East of Italy (www.parcotigli.it). As previously described the Unit follows patients from all regions of Italy, offering a rehabilitation program of 30 days for alcohol, classic drug substances (cocaine, medical products like benzodiazepines) and also NPS. "*Alice*" voluntarily asked to follow the Unit's programme including 1) detoxification phase 2) psychopharmacological and psychiatric assessment 3) group and individual psychotherapy and 4) psychomotor rehabilitation. As a main diagnosis mental services assessed Alice for cocaine dependence and a personality disorder. She arrived with an important pharmacologic treatment: sertraline (200 mg/day); valproic acid (900 mg /day); quetiapine (400 mg/day); aripiprazole (10mg/day); clotiapine (40 mg/day); lorazepam (5 mg /day); clonazepam (2 mg/day) and at her arrival she confirmed also a substantial misuse of lormetazepam. Standard blood panel and ECG were normal, with valproic acid in therapeutic range (56.9 ug/ml), while at the arrival toxicological urine sample (method KIMS COBAS) was positive to cocaine (617 ng/ml), benzodiazepines (879 ng/ml), negative to cannabis, alcohol, methadone, barbiturates, opioids; at the end of hospitalization it was positive only to benzodiazepines (416 ng/ml), negative to cannabis, alcohol, methadone, barbiturates, opioids, cocaine.

***Medical history***

"*Alice*" was a 30 year old female subject with a history of substance dependence (cocaine and alcohol), a gambling disorder and a previous diagnosis of Borderline Personality Disorder (BPD). She had no other on-going illnesses at the time. Alice came from a problematic family background: in particular at age of 8 years old her mother left the family, suffering from alcohol dependence. Alice completed her high school degree (Liceo Scientifico) and then she went to university; and at the time of the hospitalization she was concluding her thesis as nursing graduate. Her contact with public mental health service was ascribable to 2009 for an eating disorder (anorexia nervosa): she followed a day hospital cognitive behavioral treatment for few weeks, without medications. Starting from 2012 she was accessed in psychiatric ward for suicidality and depressive mood (15 days hospitalization) and for an episode of psychomotor agitation (3 days hospitalization). After that, in September 2013 she was followed by a Personality Unit for three months and then supported by local psychiatric outpatients service. After few months she was suggested for our rehabilitation program with the aim of recovery from her substances dependence, which was considered as secondary diagnosis. At the time of arrival she was not supported by a local Department of Addiction.

***Previous consumption of classic substance and NPS***

The assessment for substances was conducted through clinical interviews, collecting further anamnestic information both for 'classic' and 'novel' compounds (NPS): as a matter of fact Alice revealed here the use of synthetic cathinones and several psychoactive compounds.
At the age of 12 years old she started using cannabis (THC) and alcohol weekly for recreational purposes with her friends, then at 13 she experienced cocaine for the first time, starting a sporadic but lonely consumption. Closely related to her unstable pattern of relationships[243], Alice increased the abuse of cocaine through years, maintaining the consumption of THC and ethanol.
Starting from 18 years old cocaine and cannabis abuse decreased significantly and at the age of 20 she started going to "rave parties", consuming high dosage of club drugs every weekend: she confirmed abuse of MDMA (3,4-Methylenedioxymethamphetamine)[244] and LSD (lysergic acid

diethylamide)[245]. Patient specified that she "tried everything available, with the aim to induce hallucinations", so much so her friends "nicknamed her '*Alice*', like '*Alice in wonderland*'".

For what concerns novel compounds she reported an intense use of NPS, and specifically:

- Mephedrone[59]: she obtained this synthetic cathinones on the street market, consuming it with her friends for an entire year (2012) instead of cocaine. As modality of intake she reported nasal insufflation and smoking, 4 days per week, with a progressively higher dosage (from 0,5 grams and to 4 grams). She used mephedrone because it was a)'easily available', b) very 'cheap', with c) 'powerful stimulant effect, better and different then cocaine'. She reported in particular many 'bad tips', especially during the 24 hours comedown, with strong low mood and suicidal thoughts. Described common withdrawal symptoms were sweating, headaches and insomnia.
- Other synthetic cathinones: she reported sporadic use of several substances of this family; she only remembered the name of MDPV (Methylenedioxypyrovalerone), sold in form of crystal "bath salts"[246,247].
- Ayahuasca: she reported the ingestion of this plant brew[248] only once, describing typical delusional parasitosis (Ekbom's syndrome).
- Psychedelic mushrooms ('magic mushrooms'): ingested 3-4 times; she reported the classic psychedelic effect due to contained tryptamines (psilocybin and psilocin)[249].
- Synthetic cannabis ('Spice drugs'): she smoked compounds belonging to this wide group[55,132] four times, describing effects 'similar' to THC but more 'dissociative' and also with visual hallucinogenic effects[30]. She was not able to specifically identify ingested chemical compounds.
- Salvia divinorum: she consumed this ethno – drug[103,168,173]2 times, experimenting brief visual hallucinogenic effects and uncontrolled laugh.

***Use of mephedrone: chronology of the case***

As Table 31 shows, the intense abuse of NPS (mephedrone in particular) in Alice's case chronologically preceded accesses to psychiatric ward because of severe suicidal thoughts and psychomotor agitation. These severe psychopathological effects have been already related in several cases series as acute issues of synthetic cathinones[250], while literature seems to poor for middle and long time effects of this compound[251,252]. NPS consumption was not identified neither analytically nor when interviewing her at the time. Alice was managed with a multiple psychopharmacological treatment without psychosocial intervention (PSIs) for (novel) substance misuse.

**Table 31: Alice's history**

| | |
|---|---|
| **Childhood** | Social and family difficulties. |
| **12 years old** | First contact with substances (THC; Alcohol; Cocaine). |
| **18-20 years old** | Relationship problems, increased use of substances. |
| **22-23 years old** | Use of club drugs; searching hallucinogenic effects. |
| **25 years old** | First contact with mental health services for eating disorders. |

| | |
|---|---|
| **27 years old** | **Intense use of mephedrone and other NPS.** |
| **27-28 years old** | **3 different accesses to psychiatric ward** for depressive episode, psychomotor agitation and mood instability.<br>Multiple psychopharmacologic treatment |
| **29 years old**<br>**30 years old** | Cocaine (crack), alcohol and lormetazepam dependence,<br>Pathological gambling. |

***Assessment of the case***

On arrival the patient was interviewed with Structured Clinical Interview for DSM-IV (SCID I and II), confirming the diagnosis of Personality Borderline Disorder (BPD), fulfilling DSM-IV criteria for cocaine and alcohol dependence (corresponding to cocaine and alcohol use disorder in DSM-V[253]), and also pathological gambling, binge-eating disorder and a severe Lormetazepam dependence[254]; In the Symptom Checklist 90 (SCL-90) she obtained a score of 1.37 at the GSI scale. According with collected additional information after the recovery she received also the diagnosis of stimulants (NPS) abuse according with DSM-IV (stimulant use disorder in DSM-V) (Table 32).

| Table 32. Assessed diagnoses in Alice's case |
|---|
| Personality Borderline Disorder (BPD) |
| Cocaine and Alcohol dependence |
| Stimulants (NPS) abuse |
| Lormetazepam dependence |
| Pathological gambling |
| Binge-eating disorder |

Moreover in the 26th day of recovery MMPI-2 was used in order to assess Alice's personality with the following results.

| Table 33. Results of MMPI-2 | |
|---|---|
| Scale | t-scores (50-65) |
| L (Lie) | 54 |
| F (Infrequency) | 65 |
| K (Defensiveness) | 38 |
| Hs (Hypochondria) | 57 |
| D (Depression) | 62 |
| Hy (Hysteria) | 54 |
| Pd (Psychopathic Deviate) | 76 |
| MF (Masculinity / Femininity) | 48 |
| Pa (Paranoia) | 54 |
| Pt (Psychastenia) | 59 |
| Sc (Schizophrenia) | 68 |
| Ma (Hypomania) | 59 |
| Si (Social introversion) | 52 |
| Anx (Anxiety) | 69 |

| | |
|---|---|
| Fear (Fear) | 64 |
| Obs (Obsessiveness) | 65 |
| Dep (Depression) | 67 |
| Hea (Health) | 58 |
| Biz (Bizarre mentation) | 56 |
| Ang (Anger) | 72 |
| Cyn (Cynicism) | 51 |
| Asp (Antisocial practices) | 60 |
| Tpa (Type A) | 61 |
| Lse (Low self-esteem) | 67 |
| Sod (Social discomfort) | 47 |
| Fam (Family problems) | 67 |
| Wrk (Work interference) | 69 |
| Trt (Negative treatment indicators) | 60 |
| APS (Addiction Potential Scale) | 68 |
| ASA (Addiction Acknowledgement Scale) | 102 |

A standardized psychometric test of adult personality and psychopathology such as MMPI-2 was used here to obtain some more specific information on patient's personality and to better explore her propensity for hallucinogens and use of NPS in general.
Alice obtained the highest scores in Pd (Psychopath Deviate) scale (t=76), the well known APS (Addiction Potential Scale) and ASA (Addiction Acknowledgement Scale) scales, confirming the utility of these two derived scale for assessing substance abuse problems. MMPI-2 detected also high scores in Ang (Anger), Anx (Anxiety), Sc (Schizophrenia) and Dep (Depression) scales (see Table 33): the meaning of this peculiar profile needs to be confirmed and discussed in future research, but it suggested a complex personality profile where different pathological issues co-exist.

***Treatment***

During her recovery she participated in the detoxification program, receiving psychiatric, toxicological and personality assessment through both psychiatric and psychological interviews (2 times/day), following Unit entire program (30 days) and participating in the systemic and cognitive-behavioral group psychotherapy developed for addictions (2-3 times/days).
Specifically the MMPI-2 profile here helped physicians of the Unit in their clinical activity in order to assess correctly the case of Alice, suggesting the most critical and psychopathological areas: psychopathic deviate[255] ; schizophrenic[256] , depressive and anger[257] scales in particular. These findings in our approach, even if preliminary, could be useful to help these patients.
Indeed this report case also underlined as a multiple intoxication scenario produces difficulties in the patients' treatment. At the arrival Alice assumed a SSRI (Selective Serotonin Reuptake Inhibitor) antidepressant, a mood stabilizer, three neuroleptics, two benzodiazepines, with severe dependence on Lormetazepam. Nevertheless she was still complaining of anxiety, low mood and a sense of 'instability' self-reporting a high score in the SCL-90 scale. At the end of the recovery the medical staff recommended a psychopharmacological medication with a Serotonin-Norephinephrine Reuptake Inhibitor (SNRI), a mood stabilizer (valproic acid) and an atypical antipsychotic drug (quetiapine). Quetiapine in fact is a well know drug used for alcohol[258,259] and stimulants dependence[260] and chose here to stabilize the most critical psychopathological areas. Concerning the pathological gambling, it developed only in the last 6 months right after initiation of treatment with Aripiprazole and according with recent recommendation and evidences[261,262] this medication was

interrupted in our Unit. The final psychopharmacologic treatment was with Venlafaxine (225mg/day); Valproic Acid (900 mg/day); Quetiapine (400 mg/day) and Clonazepam[263] (1 mg/day).

After the recovery in our Unit Alice went to a local community for Dual Diagnosis.

***Final considerations on the case***

This case illustrates how NPS can become drugs of choice for their easy availability and relatively low cost in comparison to controlled compounds. As described, the misuse of NPS may occur in a multiple toxicological scenario[86], including alcohol, classic illicit drug and new addictions. In territorial services this patient was assessed for BPD, classic drugs dependence (including benzodiazepines) and pathological gambling disorder but not for club drugs and NPS. Actually in the last year her psychiatrist reported a high instability in her mood but the severe abuse of mephedrone was not identified. This anamnestic element seemed to suggest that the NPS phenomenon in Italy is still unfamiliar to healthcare professionals as they self reported in Phase 1[224]. The case, as a matter of fact, identified consumption and experimentation of different classes of compounds, including club drugs (LSD and MDMA), synthetic cannabinoids but also Ayahuasca, Salvia divinorum and psilocin: the main desired effect was here related to hallucinogenic potential of these compounds.

Briefly, Alice's case underlines:

- The presence of NPS sold as analogue compounds for other most "expansive" drugs (e.g. cocaine). Mephedrone was available in the street market as replacement of cocaine.
- The difficulties to recognize NPS abuse and the importance of a profound anamnesis in suspected multiple intoxication scenarios, where no analytical confirmation is currently possible.
- The psychiatric consequences of synthetic cathinones, in term of psychomotor agitation, depressive episodes and overall of worsening patient's symptoms and prognosis.
- The possibility to describe psychopathological profile of these new patients for example through questionnaire likes MMPI-2, in order to help and guide health professionals in their clinical activities.
- The importance of NPS management in terms of identification of problematic NPS use, structured drug treatment, psychological therapy and semi- residential treatment.
- The need to "widen the front door"[80] in existing service and units (e.g. drug alcohol teams) to assess new emerging populations of users (e.g. club drug users).
- The value of expanding awareness, knowledge and skills on NPS in term of patient's management.

**Case report n. 2: "*Paranoid android: Marvin*"**

"*Marvin*" arrived in the Dual Diagnosis Unit (Casa di Cura "Parco dei Tigli") in 2014 with a diagnosis of Substances induced Psychosis (DSM IV-R) and with symptoms of a depressive episode occurred in the last 4 weeks. When he was hospitalized in our Unit, the reality check seemed not to be impaired by active hallucinations or delusions.
Local Mental Health Service (CSM) were following Marvin for his psychotic symptoms, treating him with antipsychotic and antidepressant medications: risperidone (4mg/day), venlafaxine (75mg/day), biperiden (4mg/day) and delorazepam (2mg/day). Local drug service (Ser.D) was only aware of THC misuse in the past years.
At arrival he was compliant with his medications but unsatisfied, complaining of a generalised "lack of energy" [like the fictional character of the book "The hitchhiker's Guide to the Galaxy", the depressed robot called Marvin]. The blood panel was altered because of Cholesterol 220 mg/dl and Triglycerides 226 mg/dl, while the other parameters were normal, including the ECG. For what

concerns the toxicological urine sample (method KIMS COBAS) coherently was positive to benzodiazepines (246 ng/ml) and negative to cocaine, cannabis, alcohol, methadone, barbiturates and opioids.

***Medical history***

Marvin had no on-going illness, with negative past organic medical history; patient came from a healthy family, was 28 years old, single, studied at Liceo Scientifico (High School) and for two years attended University, faculty of Herbal Techniques.

Patient was in contact with Mental Health Service since age of 16 years old. As previous psychiatric events he reported: a 17-days hospitalisation in psychiatric ward for an intense 'anxiety' episode (2002) with final diagnosis of "psychotic episode"; an emergency room observation for one night (2014); day-hospital psychiatric monitoring and hospitalisation (15 days) before admission in our Unit (2014) due to 'delusions' and 'panic attack'. Regarding this last event Marvin did not confirm substances abuse to psychiatrists and never specified any ingested compounds in order to avoid police or legal consequences. Colleagues from the health services considered as differential diagnosis:

- bipolar disorder; due to some hypomanic episodes recorded by his parents,
- depressive episode with psychotic features; due to a self-reported low mood and energy,
- schizophrenia; due to the suspected presence of positive and negative symptoms.

Mental service suggested our semi-residential recovery after the last hospitalisation to assess the case. During psychiatric and psychological interviews Marvin described an intense use of cannabis and "skunk"[264] starting from the age of 16 years and probably inducing the first severe psychotic episode. Visual (in form of a "peripheral vision") and auditory (as "voices") hallucinations caused hospitalisation and conduced Marvin to health service with a psychopharmacological treatment (duloxetine 30 -60 mg/die; olanzapine 5-10 mg/die).
During the following years Marvin maintained contact with the service, without THC or drug specific biosocial interventions. However he also developed a high interest in ethno-botanical remedies and in Shulgin's books on synthetic compounds. Therefore at eighteen years old Marvin went to University, chose Herbal Techniques and started surfing websites and online fora describing a methodical experimentation of several compounds.

***Previous consumption of NPS and substances***

For the very first time during this recovery Marvin described his experimentation as "psychonaut". In recent years he consumed many compounds, describing their chemical names, desired effects, dosage and route of intake, demonstrating a great familiarity with the NPS galaxy. Marvin retrieved Shulgin's works and NPS information online, buying products from dedicated websites on the Internet and picking up them in the Post-Office Box. Specifically, he reported about:

- JWH 210: he smoked this synthetic THC several times in the last 4 years, obtaining sedative and dissociative effects; according with online discussions patient chose purposely this compound, never trying other spice drugs (e.g. AH families); he explained how to dissolve in alcohol the substance, obtaining single doses of 25 mg.
- 4 HO Met [4-hydroxy-N,N-ethyl-methyltryptamine]: he tried this tryptamine once, with a dosage of 15-20 mg, experimenting a spontaneous "laugh" and low mood in the comedown. Patient noted that he did not have hallucinations as expected, probably because he was taking anti-psychotic medications.
- 2 C-E [4-ethyl-2,5-dimethoxyphenethylamine]: Marvin used this phenethylamine once, at dosage of 18 mg, looking for a stimulant effect but in vain.

- MDPV [3, 4- methylenedioxypyrovalerone]: he consumed “bath salts” at low dosage two times, dissolving crystals in water; he did not remember the exact dosage but observed a middle stimulation, but not as desired.
- 3 Meo PCP [3-Methoxy-PCP]: he bought it from an online source but never tried it.
- 4 HO MIPT [4-hydroxy-N,N-methyl-isopropyltryptamine]: he bought it from an online source but never tried it.

At 20 years old he suffered from a “depressive episode” and mental health psychiatrist changed his medication to Sertraline (50mg/die) and Aripiprazole (10-15 mg/die), but Marvin felt unsatisfied and in secret continued experimenting with various substances:

- THC: Marvin consumed high dosage of cannabis every day, especially during University’s years, smoking it, using it in coffee and also in homemade bread.
- Alcohol: he exceeded in drinking during weekend; he did not develop alcohol dependence.
- Kratom: he consumed this ethno-drug once, describing as untoward effects intense sweating and “a feeling of heat”, middle visual effects (similar to visual hallucinations) and miosis. Main effect was middle stimulation, researched with a low dosage of the compound exactly as suggested in online fora (see Technical folders on Kratom).
- Amanita muscaria: he used this poisoning mushroom only once, for “curiosity”.
- Salvia divinorum: he smoked it few times, with some of the classic effects (laugh) but without hallucinations, probably due to Marvin’s psychopharmacological treatment.
- Ephedrine: he searched stimulation also with this alkaloid, stolen in the chemical lab at University. He mixed it also with pure caffeine. He used these compounds several times with a good stimulation especially to increase performance at the gym.
- Ketamine: he consumed this PCP-like compound 3 - 4 times, with a general “pleasant dissociative effect” but at the same time describing this drug “harmful” due to its strong derealisation effect.
- Methoxetamine: he also tried this ketamine analogue, at 50 mg, experiencing a strong stimulation quite different from ketamine (“another planet”, “powerful”); for few seconds he had also a psychotic experience.
- Pentedrone (α-methylamino-valerophenone): Marvin used also this cathinone, smoking it 2-3 times, but with a mild effect of arousal.
- Ethyl-phenidate: Marvin insufflated this analogue of methylphenidate with a ‘strange effect’ and dissociative symptoms. He tried this drug only one time, regretting not to consume it more.
- 25 C and I NBOMe: he insufflated also these two powerful phenetylamines twice, at unknown dosage (see Technical folder on 25I-NBOMe), obtaining a stimulant effect.
- Oxycodone: he remembered to have consumed this prescription medicine one time.
- AH-7921 and MT-45 (doxilam): he also ingested these two new opioid analgesics with morphine-like effect; these compounds were very recently available in the online market.
- DMT [N,N-Dimethyltryptamine]: Marvin used this psychedelic tryptamine once, vaporizing the substance with a mild effect and no hallucinations.
- Alpha-PVP: few months before the last psychiatric hospitalization he started using this new compound; the consumption was intensive, at a progressively higher dosage and caused severe psychotic symptoms.

**Table 34. Classic compounds and NPS consumption reported during Marvin’s recovery**

| | Compounds properties | Rating of experience |
|---|---|---|
| **THC (cannabis and hashish)** | Sedative | +++ |
| **JWH 2210** | Sedative | +++ |
| **Alcohol** | Sedative | + |
| | | |
| **2 C-E** | Stimulant | + |
| **MDPV** | Stimulant | + |
| **Pentedrone** | Stimulant | + |

| | | |
|---|---|---|
| **Ephedrine** | Stimulant | +++ |
| **Ethyl-phenidate** | Stimulant | ++ |
| **Alpha-PVP** | Stimulant | +++++ |
| | | |
| **4 HO Met** | Hallucinogenic | +/- |
| **4 HO MIPT** | Hallucinogenic | 0 |
| **DMT** | Hallucinogenic | +/- |
| | | |
| **Kratom** | Stimulation/sedation | + |
| **Amanita muscaria** | Experimentation | +/- |
| **Salvia divinorum** | Hallucinogenic | +/- |
| | | |
| **Ketamine** | Dissociative | +/- |
| **Methoxetamine** | Dissociative | ++ |
| | | |
| **Oxycodone** | Sedative | + |
| **AH-7921** | Sedative | + |
| **MT-45** | Sedative | + |

***Marvin and Alpha-pyrolidinopentiophenone (a-PVP)***

Therefore after the experimentation of many compounds through the years, Marvin discovered online fora the existence of alpha-PVP (or a-PVP, see Technical Folder) and decided to try this synthetic cathinone due to its declared stimulant properties. Patient reported an enthusiastic psychotropic effect, defining this substances as "the best compound ever tried". He pinned down this experience in details:

- Alpha-PVP was easily available in powder form through online websites (patient preferred not to reveal the name). In a few days the compound arrived in an anonymous package and in order to avoid any legal consequence Marvin gave neighbour's mail address, stealing the parcel.
- Patient insufflated or smoked alpha-PVP, every day for 3-4 days, for a period of 5-6 months.
- The dosage was progressively higher, till 300 - 400 mg. Marvin was aware that the suggested dosage in online fora was 25 - 30 mg, but he desired a strong stimulation and sexual arousal.
- He consumed this compound always alone at home; he never slept during its effects.
- Reported effects were:
  - Stimulation with mental euphoria and high levels of physical energy;
  - Sexual arousal, described as a important desired effect for the patient;
  - 'Panic attacks' with anxiety and tachycardia, especially consuming high dosage of the compound;
  - Hyperpyrexia: Marvin had a sudden sensation of heat after the ingestion of alpha-PVP, with a body- temperature of 40°C;
  - Delusions (with both visual and auditory hallucinations): especially at high dosage Marvin reported delusions and hallucinations.

At the time patient was on medications (antidepressants and neuroleptics), so it is probably relevant to report the psychotic breakdown of the case. Marvin in fact described several different episodes:

- In the first episode he started a communication with imaginary presences ("shadow people"), describing both visual and auditory hallucinations, with no insight during the experience. The dosage of consumed drug was around 100 mg.
- The second episode after the insufflation of 150-200 mg of alpha-PVP was characterized by auditory hallucinations (sort of "noises" from the bathroom plumbing) associated with persecutory delusions (to be "spied" by anti-drugs agents) that provoked him into flushing the remaining compound.

- The third psychotic experience was an Ekbom's syndrome: Marvin had the delusional belief to be infested by parasites under his skin; he took several showers to clean his body and then searched for a dermatologist. This belief was not only limited to the "trip" with alpha-PVP: also during the recovery in our unit he described the sensation of formication, fearing a sort of skin infection.
- The last described psychotic episode caused an acute hospitalisation in a psychiatric ward and then the recovery in our clinic. Marvin ingested over 200 mg of alpha – PVP, re-dosing the compound during the day, developing a persecutory delusion while walking on the street: patient became suddenly "aware of the presence of a sniper" near a bridge, perceived some "shots in his body, like a tazer" and "escaped" jumping into the river. After that he reached the Mental Heath Service and requested help and hospitalization. Marvin did not reveal consumption of alpha-PVP (he felt spied on and preferred not to "give information") and so colleagues doubted an attempted suicide.

***Assessment of the case***

During the recovery in our unit Marvin was assessed with clinical interviews in order to collect the whole anamnesis of the case, in particular for what concerned the abuse of NPS. According with our protocol the patient was evaluated with

- SCID (Structured Clinical Interview for DSM-IV) I and II; these diagnostic exams were used to determine respectively Axis I and II mental disorders and personality disorders.
- SCL-90 (The Symptom Checklist 90)[226]; a psychometric instrument to psychological problems and symptoms of psychopathology. When Marvin arrived he self-reported a global score of 1.57 at the GSI scale, suggesting a moderate level of psychopathology.
- MMPI-2 (The Minnesota Multiphasic Personality Inventory); this standardized psychometric test of adult personality and psychopathology was administered at 28th day of recovery, with these results in single scales:

| Table n 35: Results of MMPI-2 | |
|---|---|
| Scale | **t-scores (50-65)** |
| L (Lie) | 39 |
| F (Infrequency) | 720 |
| K (Defensiveness) | 36 |
| Hs (Hypochondrias) | 64 |
| D (Depression) | 76 |
| Hy (Hysteria) | 67 |
| Pd (Psychopathic Deviate) | 78 |
| MF (Masculinity / Femininity) | 60 |
| Pa (Paranoia) | 80 |
| Pt (Psychastenia) | 74 |
| Sc (Schizophrenia) | 99 |
| Ma (Hypomania) | 72 |
| Si (Social introversion) | 75 |
| Anx (Anxiety) | 66 |
| Frs (Fear) | 43 |
| Obs (Obsessivenes) | 72 |
| Dep (Depression) | 89 |
| Hea (Health) | 71 |
| Biz (Bizarre mentation) | 97 |
| Ang (Anger) | 54 |
| Cyn (Cynicism) | 59 |

| | |
|---|---|
| Asp (Antisocial practices) | 63 |
| Tpa (Type A) | 64 |
| Lse (Low self-esteem) | 90 |
| Sod (Social discomfort) | 59 |
| Fam (Family problems) | 81 |
| Wrk (Work interference) | 89 |
| Trt (Negative treatment indicators) | 79 |
| APS (Addiction Potential Scale) | - |
| ASA (Addiction Acknowledgement Scale) | - |

In this case the L-F-K pattern[265] suggests that Marvin tends to exaggerate his symptoms, making difficult to describe his MMPI-2 scales and profile. However this information is coherent with patients' history: he self perceived and declared himself "depressed" on several occasions, his psychiatrist prescribed different dosage of antidepressants and Marvin himself looked for online stimulant products. Moreover it is worth considering here that the highest score was obtained at the *Schizophrenia* and *Bizarre mentation* scales, strongly underlining presence of psychotic symptoms.

According to all gathered information (clinical interviews, psychometric instruments including MMPI-2) the final diagnoses of the case were

- Stimulant and cannabis dependences
- Psychotic episode induced by substances
- Schizoid Personality Disorder

***Treatment of the case: intense interventions***

The hospitalization in our Clinic lasted 40 days, and Marvin participated entirely in the rehabilitation programme that includes individual (2 times at week) and group (2-3 times during the day) psychotherapy, psychopharmacological assessment, and psychomotor rehabilitation.

In the very first two weeks he was "detached" and solitary during all the activities, and most important of all, he demonstrated a low insight on NPS problem; he was still determined to use alpha-PVP because of its desired effects. He required high intensity interventions on different levels with motivational interviewing, CBT based intervention and also a change in his medications. In fact the medical team introduced bupropion (150 mg/day), which is a well-tolerated second-generation antidepressant, generally, assumed to be without abuse potential, even if some reports describe a recreational use probably due to its chemical structure[144,145,266]. During the second part of the recovery Marvin started integrating into the group activities, engaging in psychotherapy activity, observing an increasing mood, experiencing new relationships with hospitalised patients and reconsidering his position on NPS.

Marvin returned home after the recovery, followed both by mental health service and drug service that were properly informed of the case.

***Final considerations on the case***

The present case report described clinical observation of a "psychonaut" patient, supported by mental services. *Marvin* reported high familiarity with NPS, experimented many substances (both classic and novel), and revealed a severe abuse of a new synthetic cathinone (alpha-PVP) with severe psychopathological consequences. A-PVP is a very recent NPS, neither banned in Italy or UK (see Technical Folder on a-PVP), with powerful stimulant effects and a high risk of re-dosing.

In particular Marvin case highlights:

- The presence of NPS misuse in young adult psychiatric population[85] and the wide compounds experimentation amongst specific groups (e.g. psychonauts).
- The difficulty in standard clinical settings to identify NPS; local drug service was aware only of THC consumption.
- The reported effects of alpha-PVP as a powerful stimulant and sexual enhancer; a-PVP acts at "standard" and higher dosage (200-300 mg) with a relevant risk of re-dosing.
- The report of a-PVP untoward medical effects and psychopathological symptoms (from anxiety, insomnia to psychotic episodes); these occurred in a psychiatric patient in treatment with neuroleptics and antidepressants.
- The potential high risk of severe psychotic symptoms due to a-PVP.
- The first attempt to describe through psychometric instruments (MMPI-2) the profile of an Italian "psychonaut"[267]; future research needs to better describe personality of these emerging groups.
- The need of more intense psychosocial intervention in case of recovery and rehabilitation programme for intense NPS users; motivational interviews, CBT intervention, group and individual psychotherapy were here fitted to the patient's need.
- The importance to understand the desired effect searched by users as self-treatment beyond recreational purpose: collecting information on previously consumed NPS may be important as well for psychopathological profiling.

## CONCLUSIONS

The diffusion of NPS is a threat for public health and a new challenge for all healthcare and other professionals, who are unprepared to face this new and rapidly expanding phenomenon.

The first Phase of this research study started in 2011 exploring the level of knowledge and awareness of NPS amongst a sample of Italian healthcare professionals.
The recruited sample was mainly constituted by experienced doctors from Psychiatric and Addiction services with good informatics skills. Although various attempts were made to involve Paediatric and Emergency departments, a very limited number of responses were received, suggesting the need of additional efforts for inclusive studies in the future in order to increase their awareness of NPS.
Overall, participants declared minimal levels of expertise with self-rating technical knowledge on NPS "poor" or "basic" in the majority of the cases (61%) and a relevant percentage of them never asked patients about the consumption of novel compounds (26.7%). Conversely, at the time the phenomenon seemed not to be so rare in Italy: in fact an 18.1% of interviewees was involved in care of NPS misusers. A concerning result was that a high percentage of the sample did not have any knowledge of the most diffuse NPS listed in the survey questionnaire, such as "spice drugs" (synthetic cannabinoids) (26.5%), mephedrone (27.9%) and Salvia divinorum (25.7%). This is rather surprising because these compounds were already under regulation by national law since 2011. This evidence also suggests the need of more effective governmental communication on novel substances warned or banned by national and international agencies (e.g. DPA, EMCDDA, UNODC). Even if respondents did not know various NPS listed in the survey, they perceived the issue as highly relevant to their professions (96.1%) and as a risk factor for many medical/psychiatric symptoms, such as psychomotor agitation (75.7%), psychotic and affective disorders. Interviewees had particular concern about assessment (75.7%) and treatment (74.5%) in emergency settings where errors might occur. They indicated the need to receive additional information asking for more reliable and up-to-date data disseminated through emails (70%), dedicated websites (51.9%), specialised newsletters (40.3%), Facebook pages (14%) and other more personalised channels offered by the ReDNet project.

In 2013 the second Phase of this project evaluated the outcomes of European ReDNet initiative through an online survey that reached registered professionals in 22 countries, including Australia, Canada, USA, Ghana, Kenia, Mexico and Taiwan.
Interviewees were mainly physicians and researchers, with a good experience in their field, mostly working in Italy and the UK, mainly in hospitals/drug-alcohol action teams and Universities; however it is worth noting that the interviews collected among the ReDNet mailing list, reached also other health professionals (nurses, psychologists, social workers, etc.), government professionals, law and enforcement officers, journalists: all figures working at different levels in the NPS field.
A high percentage of the surveyed sample recognised patients who used NPS (69.6%): even if this result was not statistically comparable with Phase 1, it can suggest that the ReDNet dissemination tools helped registered clinicians in their activity. In fact the most used technological resources (website [48.5%], newsletter [31.9%], SMAIL service [17%]) permitted the dissemination of academic papers (34.1% of preferences), technical folders and conference materials. Resources provided by ReDNet were mainly used to self-educate on NPS (52.6%) and expand awareness on new emerging issues (48.5%): provided data was judged up-to-date (46.7%), reliable and objective.
The SMAIL service, the latest tool developed by the ReDNet project for professionals, was particularly relevant internationally. During the pilot period registered users, based in the UK and Italy, searched information both on NPS and classic substances, suggesting a low acquaintance with their definition. Furthermore in 47.5% of cases the inquiries regarded unknown products or substances available on the market. Beyond SMAIL errors in the recognition system, these results highlighted difficulties in the naming of the NPS galaxy: novel compounds in fact might have a

standard, chemical, trade and slang name amongst misusers, which is a real issue for professionals[268].

Phase 3 of this research project underlined the clinical impact of NPS and included the preparation of four Technical Folders and two clinical studies collected from patients I encountered during my clinical activity as psychiatrist.
The first Technical Folder was about a powerful and dangerous synthetic phenethylamine (Bromo-dragonfly), which caused several deaths in recent years and had a high hallucinogenic potential due to its chemical structure; the second Technical Folder was about a stimulant novel phenethylamine (25I-NBoMe) reported also in one of the clinical case (*Marvin)*; the third Technical Folder was on Kratom, a herbal product originally from Southeast of Asia with a use in traditional societies, but that has became popular also in Europe and USA in recent years; the last Technical folder was on alpha-PVP, a new powerful synthetic cathinone warned by EMCDDA and UNODC last year, also reported in the second case study presented here.
The two clinical cases highlighted how NPS recognition can change patients' life. The case of Alice clearly described how novel compounds are used as an alternative to controlled substances, causing unpredictable effects, worsening of psychiatric disturbances (e.g. psychomotor agitation and suicidal thoughts), and provoking a difficult management of these patients by traditional services. The second case (*Marvin*) reported difficulties of standard clinical settings to identify a patient with an intense abuse of a new drug (alpha-PVP), severe psychotic symptoms and also a large previous experimentation of online products and compounds. Both clinical reports also analysed personality and psychopathological profile of two new emerging populations (club drug users and psychonauts) using MMPI-2. Further investigations are needed in this direction.
Thus, collected cases show clearly how mental and drug services have difficulties to identify, recognise and manage NPS misusers, seemingly to be unprepared explorers in this expanding galaxy.

**Phase 1, 2 and 3: methodological major limits and observations**

From a methodological point of view the study presented some important limits, which must be considered in future initiatives. A main problem was the necessity of keeping pace of such novel and unknown phenomenon: for example, as described in the background section, between 2010 – 2014 the definition of NPS itself has changed, including different class of compounds and reaching to an international agreement on the term; hence, also this project needed to adjust to this "everchanging" galaxy for example including or excluding some compounds, according to this definition or to novel legislations.

Regarding Phase 1, data on other European countries were not available, even if collected during the ReDNet project. Therefore there was not the possibility of comparing the Italian sample with other countries. Secondly the Italian survey was designed as a questionnaire aimed to highlight NPS expertise in Italy, and the recruitment did not permit to estimate a precise response rate for two main reasons: 1) when the link was sent to healthcare professionals of each Department was not possible to collect single e-mails due to the privacy settings of the study, and Departments, in most of the cases, were not able to quantify contacted professionals 2) when the DPA was involved, it was impossible to calculate the exact distribution of the survey in Italy.
The evaluation of ReDNet (Phase 2) collected opinions of registred professionals mainly from Italy, even if the questionnaire was designed for European ReDNet participants. Moreover, the response rate, considering the mailing list was modest (27%). This result could be influenced by the short period of time during which the survey was available (4 months), and the fact that the ReDNet project had many Italian partners and collaborators. Furthermore, the modest response from other European countries suggested treating our results with caution, even if they were numerous. Other options to evaluate the ReDNet project could be more effective (e.g. describe how the project

contributed to “fill a gap in the knowledge – base” in single Department/Unit which registered to ReDNet) but probably considered them more expensive, prolonged and partial than a single online survey able to reach all registered professionals.
Another important point is that, even if an overlapping could be reasonably speculated, the (Italian) samples of Phase 1 and 2 cannot be compared. An interesting observation is that this research work could be described as an evaluation of NPS in Italian health services before (2011) and after (2013) the ReDNet initiative, even if the main research question in Phase 2 was different.
As the results of SMAIL (Phase 2) widely suggest, a very key problem is the identification of new products in clinical field: in the 45.7% of cases the SMS – Email system could not help psychiatrist because the composition of the product was not clearly identifiable due to its slang-names or novelty. This is clearly a limit of the tool, but underlined how the identification of NPS is difficult during healthcare professionals activity, and suggest more effort in future research to support their work (e.g. urine sample screening test for class of compounds).

At the same way, the Technical Folder (Phase 3) can be very helpful to clinicians and researchers but this approach has some limits. Their methodology first of all starts when enough information on a novel substance is available, and in many cases (see SMAIL) this is not the case. Many compounds appear in the market both with chemical and slang names completely unknown, with no information on their active constituents and partial/uncomplete descriptions even in drug fora, meaning no possibility to report a specific and reliable Technical Folder.
Secondly, contained information must be treated with extreme caution when their source is anecdotal without any scientific confirmation: this could mean, for example, that a) a product may not contain the declared ingredients or be contaminated with other substances (see the case of Kratom), b) a compound has been described with a “safer” profile than other of its class (e.g. methoxetamine) or simply that c) supposed effects are quite different when consumed.
On the other hand even if partial, such information could be effective in clinical field at least to understand if an ingested NPS is a stimulant, hallucinogenic, dissociative or sedative substance (see next chapter), suggesting reported acute risks (e.g. in a emergency setting) or avoiding unappropiate diagnosis and treatments (e.g. acute psychotic episodes induced by NPS).

Finally, in clinical cases presented here, the identification of NPS misuse has been conducted in a very specialized setting (Dual Diagnosis Unit), which is not always possible with outpatients or in Emergency Rooms, and, moreover, without an analitycal confirmation of the consumption of these compounds. Future approaches to NPS users should a) investigate new laboratory tests b) clarify how to intercept these patients (e.g. with prevention programs aimed to specific populations) c) examine the possibily of psychometric instruments to support clinical activity (e.g. MMPI-2) d) develop specific guideline of intervention to guide their recovery.

**Future: exploring the NPS Galaxy through innovative tools**

According to the findings of this study there is an urgent need to inform health and other professionals on NPS. More specifically, a successful initiative should consider the following elements:

1. Have an online interface: the web is an important first line source for information on NPS (online fora, websites) and the presence of an authoritative channel of dissemination appears to be essential. Future projects should consider websites, Facebook pages, Twitter accounts and other applications as a part of the same platform with the aim of disseminating reliable information on NPS for health professionals internationally.
2. Incorporate Technical Folders on new substances when dealing with professionals: in particular physicians, should be warned on NPS chemical structure, appearance, intake, recreational use, pharmacological characteristics, toxicological, psychoactive and medical effects, including

suspected or related fatalities. Data should include trade and slang names of products in order to identify each compound in clinical field.

3. Maintain constantly up-to-date Technical Folders: including new evidences, national/international warnings, global legal status and new nicknames and street names (see Phase 2). Such an aspect requires multidisciplinary and combined efforts from research teams, which are essential to face the NPS phenomenon.
4. Produce peer-review scientific literature, conferences and educational events: interviewed professionals seemed to appreciate also more "traditional" channels of communication, important to be considered more authoritative in the field.
5. Have worldwide partnership both with national and international agencies: as described in Phase 1 and 2, a European initiative like ReDNet was able to reach professionals and researchers from very different countries. A prevention project on NPS needs to be as more international as possible, because NPS are a worldwide problem for public health.
6. Develop more targeted communication strategies for different groups of medical doctors: psychiatrists of Mental Health Services, physicians of Departments of Addiction, Paediatrics and Emergency Rooms doctors or General Practitioners should be individually informed. As a matter of fact they have different specialities and their own clinical perception of the phenomenon. Awareness on NPS should be increased at many levels and in many areas as, for example, sexual health services in the UK.
7. Develop targeted communication strategies for other specific healthcare professions (nurses, psychologists, social workers, educators, etc.), operators (including governmental professionals, law and enforcement officers, journalists, teachers) and, last but not least, academic researchers. All these figures in fact probably need different levels of information on NPS; therefore a project should be able to calibrate information according to each professional profile.
8. Develop specific communication strategies towards users: dissemination on NPS includes also targeting emerging populations who do not use traditional drug service, such as club drug users and psychonauts (see Phase 3).
9. Develop original and technological tools to help health professionals not to be lost into the NPS galaxy: as the pilot experience of SMAIL suggested, a service or an Internet-based application could be used as a "close to hand" tool in order to a) request information b) warn on new products c) mapping the phenomenon c) receive update.
10. Support health professionals in the field: as the case reports tried to describe, NPS users are difficult to identify, have a multiple intoxication scenario (which include both classic and novel compounds) and, sometimes, severe psychiatric consequences.
11. Guide health professionals in terms of more specific psychosocial interventions during recovery and rehabilitation programmes, which have been traditionally developed for alcohol and classic illicit drug use.
12. Inform health professionals on the psychopharmacological treatment of these patients: the main aim here is to support clinicians to reduce the acute and chronic harm of NPS.

Due to the astonishing multitude of available substances, a core element emerging from this study is the need to provide up-to-date and more structured information on NPS. Professionals need to better understand, foresee effects of these compounds and manage misusers, considering the absence of specific guidelines on the subject until now, although the first clinical guidance has recently been released in the UK[225].

As a matter of fact, in this research project clinicians appeared to be marginally aware of NPS-related risks, poorly informed on their chemical differences, and sometimes even confused on the nature of various compounds. As it emerged from Phase 1 and Phase 2 (SMAIL results in particular),

professionals are uncertain about the NPS families, names, classification and differential diagnosis with more traditional drugs. Further, especially in psychiatry, colleagues seem to commit errors in the assessment phase when patients consume (classic) substances[209]: in future years the problem of dual diagnosis is going to increase considering both classic illicit drug and more recent NPS appearance in the online market.
The challenge posed to them in this sense is immense. Services, in fact, are called to be well aware and informed, promptly recognize misusers, assess correctly patients and manage them with specific interventions in order to reduce harm.

For this reason more effective communication strategies able to inform but at the same time to "map" the expanding galaxy of these heterogeneous groups of compounds should be realised.

For example future initiatives on NPS should try to develop a general/synthetic overview of NPS, a "hitching guide" considering not primarily their different endogenous signaling system or chemical structure, but including at least four main polarities (Figure 40).

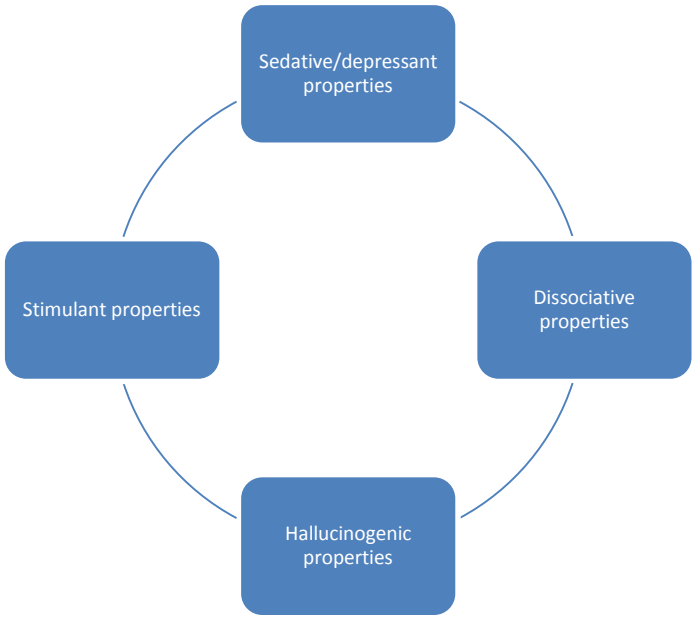


**Figure 40: Four descriptive polarities for NPS.**

These polarities could help to map the galaxy, being clearly understood in a more visual and direct way:

1) *Stimulant properties*: when a drug can induce a sympathetic nervous system arousal[269], with a so-called "fight or flight" syndrome. Despite some overlapping similarities, stimulants cannot be easily categorized by their chemical structure, mechanism of action or abuse potential. In fact many substances act in first place with this effect, releasing and/or inhibiting the reuptake of monoamines, primarily norepinephrine (NE) and dopamine (DA): for example cocaine, phenethylamines (amphetamine and other NPS), synthetic cathinones (see Technical Folder on a-PVP and *Marvin* case report) or –phenidate compounds.
2) *Hallucinogenic properties:* when a drug causes profound distortions in a person's perceptions of reality (visual and auditory hallucinations). Most of hallucinogens act through the serotonergic system[270] and classic compounds[271] are tryptamines (including psilocin, DMT and novel tryptamines), lysergamines (LSD) and some phenethylamines (e.g. Technical Folders on Bromo-dragonfly and 25I-NBoMe). However many other agents can produce similar effects acting on

different receptors systems (for example the opioid-κ agonist salvinorin A, the dissociative compounds of PCP-like family, or the brew called Ayahuasca).

3) *Dissociative properties:* when a drug produces a subjective anomaly of self-awareness (depersonalisation) and/or experience of unreality of the external world (derealisation).[272] Many substances can induce similar effects at different doses, acting on various systems (e.g. alcohol, barbiturates, cannabis and novel synthetic cannabinoids, piperazines, or some medical products and ethno drugs). PCP-like compounds, like ketamine (or methoxetamine) are exemplifying for dissociative drugs: they can induce the feeling of detachment from the environment and self[273], even with hallucinations.
4) *Sedative and depressant properties*: when a drug induces a CNS inhibition with effects from sedation to comatose state[274]. Such properties again are mediated by several different neurochemical systems (like GABA or opioids receptors) and many drugs can exhibit sedative/depressant effects, for example narcotic analgesics like morphine or synthetic opioids, alcohol, benzodiazepines, GHB or ethno drugs (see Technical Folder on Kratom).

A preliminary draft of this approach is presented below in order to show a "map" with some examples. The position of each NPS has here organized according with the information collected in the introductive chapter of this work, but constitutes only an suggestion for future approach.

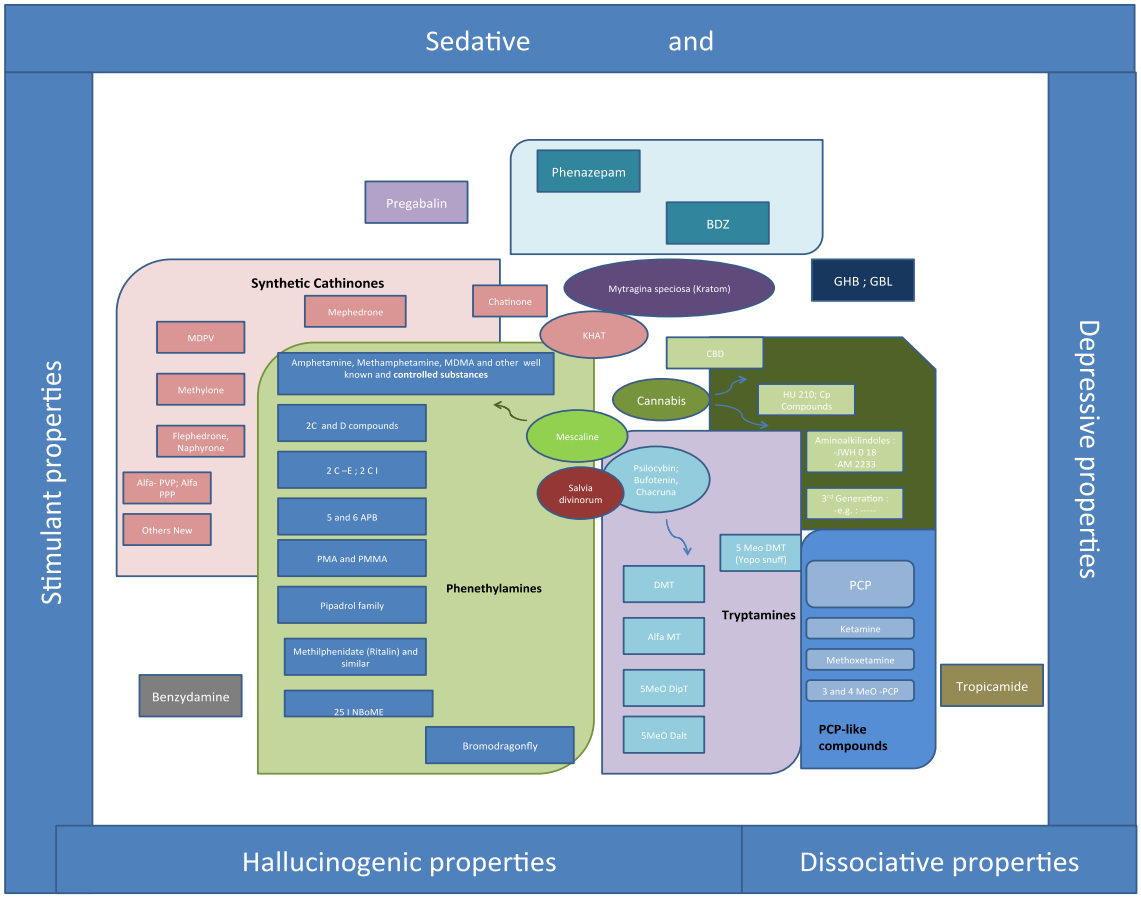


**Figura 41: A preliminary visual approach to the NPS galaxy.**

This framework, even if not exhaustive, could be useful to non-confident professionals; ideally, it should also be implemented with the aid of technological tools, such as smartphone applications, to guide professionals to a) easily identify a NPS within its family, even if its effects can differ (as we illustrated in Technical Folders) b) correlate its affinity with other more known compounds, which could be chemically different but with mimetic properties c) rapidly inform and help clinicians in the field to foresee[31] its medical effects, toxicity and psychopathological disturbances d) integrate available information on NPS to fully describe a "single constellation" of the galaxy.

In conclusion, such an innovative framework supported by a technological platform would help not only to expand awareness among health professionals, but also to build competence and best practices, especially when dealing with NPS users. As previously described, those seeking help include clubbers and "psychonauts" (see Case Reports in Phase 3), psychiatric patients, but also professionals and students or LGBT communities. They are not "classic abusers" and find difficulties in consulting and sharing their experiences with "unprepared" drug treatment services. Psychiatrists, physicians and other professionals will need such a support to explore the NPS expanding galaxy in a more effective and rapid way.

# Appendix 1

**ReDNet Survey of Health Professionals**


The ReDNet Research Project is an EU funded project which investigates optimal ways of providing up-to-date, reliable and accurate information of 'legal highs' (*) to professionals across Europe using Information and Communication Technologies (ICTs) like email or SMS (more information at www.rednetproject.eu).
We are currently developing and testing various ICT tools and identifying what information is needed, but would like to hear from you what might work best for you. To develop successful and useful tools, we need input from our potential users! Please answer as many questions as possible. All data will be collected anonymously.

(*) The term '**legal highs**' in this document refers to a class of relatively new drugs used for recreational purposes, often as legal substitutes for more common illicit drugs. These include for example Mephedrone, Spice, GBL, and Salvia divinorum that are, or when they emerged onto the drug market were, not controlled by relevant drug legislation.

---

## Personal information

**1. Are you?** (1) Male (2) Female

**2. How old are you?** _____ (Years)

**3. What is your current position?**

| *Nurse* | *Social worker* | *Psychologist* | *Physician* | *Psychiatrist* | *Educator* | *Other (specify)* |
|---|---|---|---|---|---|---|
| | | | | | | |

**4. How many years have you worked in your current position?** _____ (Years)

**5. Location of place of work:** _____ (Town)

**6. How would you consider your IT skills?** *(please circle)*

*(1) Poor* *(2) Basic* *(3) Intermediate* *(4) Good* *(5) Very good*

## About 'legal highs'

**7. How would you consider your understanding/knowledge of 'legal highs'?** *(please circle)*

*(1) Poor* *(2) Basic* *(3) Intermediate* *(4) Good* *(5) Very good*

**8. Do you see patients/clients who use 'legal highs'?**

*(1) Yes* *(2) No* *(3) Don't know* *(4) Not applicable*

**9. How many patients/clients using any drug did you see in the last 6 months?**
[_____] (if not known estimates are fine)

**10. Of these, how many patients/clients using 'legal highs' did you see in the last 6 months?** [_____] (if not known estimates are fine)

**11. Of the people using 'legal highs', how many did also use illicit drugs?**
[_____]

**12. What are the 'legal highs' used among your patients/clients? (please tick all that apply)**

| | Yes | No | Never heard |
|---|---|---|---|
| **Salvia divinorum** | | | |
| **Spice drugs (n-joy)** | | | |
| **Mephedrone** | | | |
| **Methylone** | | | |
| **Flephedrone** | | | |
| **MDPV** | | | |
| **BZP** | | | |
| **Kratom/Mytragina speciosa** | | | |
| **GBL, GHB, 1,4-butandiol** | | | |

| | | |
|---|---|---|
| **Deliah Blue** | | |
| **Bk-MBDB/Butylone** | | |
| **Bromo Dragonfly/B-fly** | | |
| **Naphyrone (NRG-1)** | | |
| **NRG-2** | | |
| **E-3PO (Blue Max)** | | |
| **6-APB (Benzo fury)** | | |
| **Other drugs (specify)** | | |

**13. Please rate how relevant is your understanding/knowledge of 'legal highs' in relation to your work?**

***Not important (1) - Very important (5)***

[_____]

**14. How would you rate the importance of these following items to get an understanding/knowledge of 'legal highs'?**

***Not important (1) - Very important (5)***

1. Overview [_____]
2. Key points [_____]
3. Chemical characteristics of active constituents [_____]
4. Appearance [_____]
5. Available information on purchase price [_____]
6. Modalities of intake (eg snorted, intra venous) [_____]
7. Legal status [_____]
8. Current use/medicinal use [_____]
9. Information on recreational use/misuse in the E.U. (or elsewhere) [_____]
10. Use in combination with other compounds [_____]
11. Pharmacological characteristics [_____]
12. Toxicological effects [_____]
13. Desired psychoactive effects [_____]
14. Side effects [_____]
15. Psychopathological disturbances associated with its use [_____]

16. Clinical advice [_____]
17. Related fatalities [_____]
18. Preventing overdose [_____]
19. Overdose management [_____]
20. Other (specify)_____ [_____]

**15. How would you rate the importance of the following items to get an understanding/knowledge of 'legal highs'?**

***Not important (1) - Very important (5)***

21. YouTube videos [_____]
22. Google search trends [_____]
23. Online marketing/selling strategies [_____]
24. Bibliography [_____]
25. List of websites that provide further information [_____]
26. Second Life

**16. Do you currently receive information about 'legal highs'?** *(1) Yes* *(2) No*

**17. If Yes, from which organizations/sources (eg TalkToFrank, DrugScope, Erowid)?**

**18. How do you receive this information?** (please circle all that apply)

a) Email *(1) Yes* *(2) No*

b) SMS/MMS *(1) Yes* *(2) No*

c) Website/s *(1) Yes* *(2) No*

d) Electronic newsletter *(1) Yes* *(2) No*

e) Professional literature *(1) Yes* *(2) No*

f) From colleagues *(1) Yes* *(2) No*

g) From drug users *(1) Yes* *(2) No*

h) Media (TV, newspapers, radio etc) *(1) Yes* *(2) No*

i) Conference /Seminars / Workshop

i) Other means (specify) *(1) Yes* _____

**19. If you do NOT have access (or have limited access) to information on legal highs, would you like to receive up-to-date and reliable information?**

*(1) Yes* *(2) No*

**20. If Yes, how would you like to receive it (select only three)?**

| | | |
|---|---|---|
| a) Email | *(1) Yes* | *(2) No* |
| b) SMS/MMS | *(1) Yes* | *(2) No* |
| c) Website/s | *(1) Yes* | *(2) No* |
| d) Electronic newsletter | *(1) Yes* | *(2) No* |
| e) Twitter | *(1) Yes* | *(2) No* |
| f) Virtual training environment (eg Second Life) | *(1) Yes* | *(2) No* |
| g) Facebook | *(1) Yes* | *(2) No* |
| h) Other means (specify) | *(1) Yes* _____ | |

**21. Would you be interested in testing any of the applications listed above that we are developing?**

*(1) Yes* *(2) No*

If so, please join our mailing list at www.rednetproject.eu

**22. Any other comments:**

**Many thanks for completing the survey.**

**The ReDNet Research Team**

## Appendix 2

**Recreational Drugs European Network (ReDNet)**

**Sondaggio ReDNet sulle Smart Drugs per gli Operatori Sanitari**

Il progetto di ricerca ReDNet è un progetto finanziato dalla Commissione Europea che indaga la modalità ottimale di fornire aggiornamenti e informazioni affidabili e precise sulle ***smart drugs***, note anche come ***legal highs*** ai professionisti europei che operano in ambito sanitario, utilizzando le Tecnologie di Informazione e Comunicazione (TIC) come e-mail o SMS (per maggiori informazioni: www.rednetproject.eu).

Attualmente stiamo sviluppando e sperimentando diversi strumenti TIC, ma vorremmo sapere quali potrebbero essere le informazioni che maggiormente possono servirvi. Per sviluppare strumenti utili ed efficaci, abbiamo bisogno di dati dai nostri potenziali utenti. Si prega di rispondere a quante più domande possibile. Tutti i dati saranno raccolti in forma anonima.

*Il termine "**smart drugs**" e "**legal highs**' in questo questionario identifica una classe relativamente nuova di droghe e sostanze ad uso ricreazionale, spesso utilizzate come sostituti "legali"delle più comuni droghe d'abuso illecite. Sono incluse ad esempio: Mephedrone, Spice, GBL, Salvia Divinorum, etc, le quali emergono nel mercato, anche online, quando non controllate da una opportuna legislazione.

---

**Informazioni Personali**

**1. Lei è** (1) Maschio (2) Femmina

**2. Quanti anni ha ?** _____

**3. Città in cui opera :** _____

**3. Quale è la sua attuale qualifica e dove attualmente lavora?** *(segni e completi)*

| Posizione | Infermiere | Medico Specialista in | Medico Specializzando in | Medico / Medico Medicina Generale | Psicologo | Ass. Sociale | Educatore | Altro (specifica) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |

| Area | Psichiatria CSM | Psichiatria SPDC | SERT | Ambulatori Medici (Privato/ Pubblico) | Pediatria Ambulatori Pediatrici | Pediatria Pronto Soccorso Pediatrico | Pronto Soccorso | Altro (specifica) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |

**4. Da quanti anni lavora con tale qualifica? _____ (anni)**

**5. A quale livello considera le sue abilità con strumenti informatici (ITC)?** *(segnare)*

*(1) Povere (2) Base (3) Intermedie (4) Buone (5) Molto Buone*

**In merito alle "Smart Drugs" o "Legal Highs"**

**6. Come considera la sua conoscenza delle "smart drugs" o "legal highs"?** *(segnare)*

*(1) Povera (2) Base (3) Intermedia (4) Buona (5) Molto Buona*

**7. Ha in carico/cura pazienti che fanno uso di "legal highs"?**

*(1) Si (2) No (3) Non saprei (4) N.A.*

**8. Negli ultimi 6 mesi quanti pazienti ha visto che utilizzano una o più sostanze d'abuso?**

(N=.....)

| | Si | No (ma mi è nota) | Non nota (non l'ho mai sentita) | | Si | No (ma mi è nota) | Non nota (non l'ho mai sentita) |
|---|---|---|---|---|---|---|---|
| **Salvia (Salvia divinorum)** | | | | **GBL, GHB, 1,4-butanediol** | | | |
| **Spice** (JWH-018, herbal smoke) | | | | **Deliah Blue** | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Mephedrone**(4-MMC, drone, meow) | | | | **Butylone** (bk-MBDB, B1) | | | |
| **Methylone** (bk-MDMA, M1) | | | | **Bromo Dragonfly** (B-fly) | | | |
| **Flephedrone** (4-FMC) | | | | **Naphyrone (NRG-1)** | | | |
| **MDPV** (Super coke, Peevee, Magic) | | | | **NRG-2** | | | |
| **BZP** (Benzypiperazine) | | | | **E-3PO** (Blue Max) | | | |
| **Kratom** (Mytragina speciosa) | | | | **6-APB** (Benzo fury) | | | |
| | | | | **Altra (specificare)** | | | |

**9. Di questi quanti pazienti facevano uso di "smart drugs" o "legal highs" negli ultimi 6 mesi?**

(N=.....)

**10. Quanti tra i fruitori di "smart drugs", nella sua esperienza utilizzano anche altre sostanze d'abuso illecite?**

(N=.....)

**11. Quali sono le "smart drugs" utilizzate, in base alla sua esperienza?** *(segnare tutte le opzioni attinenti)*

**12. Ritiene che la conoscenza di questa categoria di sostanze possa essere rilevante nella sua attività?** *(segnare)*

*(1) Per nulla (2) Poco (3) In parte (4)Abbastanza (5) Molto rilevante*

**13. In base alla sua esperienza clinica, l'utilizzo di sostanze come le "smart drugs" :**

***Non Rilevante (1) – Molto Rilevante (5)***

1. È preceduta da disturbi psichiatrici della sfera ansiosa 1—2 —3—4—5
   - Se si, quali? _____
2. È preceduta da disturbi psichiatrici dell' umore 1—2 —3—4—5
   - Se si, quali? _____
3. Slatentizza disordini psichiatrici della sfera ansioso depressiva 1—2 —3—4—5
4. È legata alla presenza *lifetime* di Disturbi di Personalità (asse II del DSM IV)

1—2 —3—4—5

- Se si, quali? _____

5. Andrebbe indagato all'esordio di disturbi nella sfera psicotica 1—2 —3—4—5
6. Andrebbe indagato nei casi di agitazione psicomotoria 1—2 —3—4—5
7. Rende difficoltoso l'inquadramento diagnostico di eventuali disturbi psichiatrici 1—2 —3—4—5
8. Rende difficoltosa la gestione di protocolli delle emergenza mediche in PS 1—2 —3—4—5
9. Rende più complesse la scelte farmacologiche nei pazienti 1—2 —3—4—5

**14. Quanto considera importanti i seguenti punti per migliorare la sua conoscenza sulle smart drugs?**

***Non Importante (1) – Molto Importante (5)***

1. Overview – Rassegna del prodotto 1—2 —3—4—5
2. Caratteristiche chimiche dei principi attivi 1—2 —3—4—5
3. Aspetto "commerciale" del prodotto 1—2 —3—4—5
4. Informazioni dipsonibili sul prezzo d'acquisto 1—2 —3—4—5
5. Modalità di assunzione (intravenosa, inalazione, etc) 1—2 —3—4—5
6. Status legale 1—2 —3—4—5
7. Uso corrente della sostanza e eventuale impiego medico 1—2 —3—4—5
8. Informazioni sull'uso/abuso ricreazionale (prevalenza) 1—2 —3—4—5
9. Utilizzo in associazione con altri composti 1—2 —3—4—5
10. Caratteristiche farmacologiche 1—2 —3—4—5
11. Effetti tossicologici 1—2 —3—4—5
12. Effetti psicoattivi ricercati 1—2 —3—4—5
13. Effetti collaterali 1—2 —3—4—5
14. Manifestazioni psicopatologiche associate 1—2 —3—4—5
15. Avvertenze Cliniche (sindrome astineziale, prevalenza) 1—2 —3—4—5
16. Possibili decessi correlati 1—2 —3—4—5
17. Informazione sulla prevenzione dell'overdose 1—2 —3—4—5
18. Gestione clinica dell'overdose 1—2 —3—4—5
19. Altro (specificare)_____ 1—2 —3—4—5

**15. Quanto considera importanti i seguenti punti per migliorare la sua conoscenza sulle smart drugs?**

***Non Importante (1) –Molto Importante (5)***

27. Filmati su YouTube 1—2 —3—4—5

28. Distribuzione delle ricerche online Google 1—2 —3—4—5
29. Strategie di commercializzazione online del prodotto 1—2 —3—4—5
30. Bibliografia correlata 1—2 —3—4—5
31. Elenco di siti web in grado di fornire ulteriori informazioni 1—2 —3—4—5

**16. Attualmente ha a disposizione informazioni in merito alle "smart drugs" o "legal high**

*(1) Si* *(2) No*

**17. In caso affermativo, da quale fonte / organizzazione le riceve ? (eg Istituto Superiore di Sanita', rapporto OEDT, Erowid, Drugscope etc…)?**

**18. In che modo riceve queste informazioni?** (segnare tutte le opzioni più adatte)

a) Email ☐
b) SMS ☐
c) Siti Web ☐
d) Newsletter ☐
e) Letteratura scientifica ☐
f) Da colleghi ☐
g) Da consumatori di sostanze d'abuso ☐
h) Media (TV, giornali, radio etc) ☐
i) Congressi/ Corsi di formazione ☐
l) Corsi Online/Second Life ☐
m*)* Altro (specificare) ☐_____

**19. Se non ha accesso o accesso limitato ad informazioni sulle "smart drugs" , vorrebbe ricevere aggiornamenti e informazioni affidabili?**

*(1) Si* *(2) No*

**20. Se si ,in che forma vorrebbe riceverle?** *(selezionare 3 opzioni)*

a) Email ☐
b) SMS ☐
c) Siti Web ☐
d) Newsletter ☐
e) Twitter ☐
f) Corsi Online , Second Life ☐
g) Facebook ☐
h) Altre (specificare) ☐_____

**20. Altri commenti od osservazioni:**

**21. Sarebbe interessato a testare alcuni degli strumenti e degli applicativi sopra elencati che stiamo sviluppando?** *(1) Si* *(2) No*

In caso affermativo si registri alla nostra mailing-list, visitando il nostro sito www.rednetproject.eu (Online: in caso affermativo inserisca qui il suo indirizzo mail)

**Molte grazie per aver completato il questionario.**

**ReDNet Research Team**

# Appendix 3


April 2013

ReDNet Project
Department of Pharmacy
University of Hertfordshire
Health Research Building
College Lane Campus
Hatfield, Herts.
AL10 9AB
United Kingdom

Dear colleague,

**Evaluation of the ReDNet project**

We are preparing a case-study to illustrate the impact of our ReDNet research and related activities. In order to demonstrate this impact we need to provide information about which of the resources/outputs produced by the ReDNet project are/were used, by whom and for what purpose(s), and what difference(s) result from their use.

We would be very grateful if you could take 2-3 minutes to complete and return the attached questionnaire or complete it online.

All responses received will be retained in a secure and confidential manner. They may be used for internal evaluation. The quantitative information provided will be initially aggregated into summary statistical data. Any comments made may be incorporated into the case-study anonymised, if necessary, prior to publication by the Funding Councils.

Thank you for your co-operation and support.

Yours faithfully,

**Prof Fabrizio Schifano**, ReDNet Principal Investigator
**Dr Ornella Corazza**, ReDNet Co-Principal Investigator, Project Manager
**Mr John Corkery**, Research Centre Coordinator

1. Your occupation *(please tick)*:
   [ ] Physician
   [ ] Nurse
   [ ] Researcher
   [ ] Law enforcement officer
   [ ] Educator
   [ ] Psychologist
   [ ] Psychiatrist
   [ ] Other, please specify: …….....

2. Age:

3. Gender *(please tick)*:
   [ ] Male
   [ ] Female

4. How many years have you worked in your current position? …….

5. Country:

6. Type of organisation *(please tick)*:
   [ ] University
   [ ] Hospital
   [ ] Government Department/Agency
   [ ] International Organisation
   [ ] Professional Body
   [ ] Charity/Third Sector
   [ ] Drug/Alcohol Action Team or similar
   [ ] Police, Probation, Law Enforcement Agency
   [ ] Education, School, etc
   [ ] Other, please specify: .....

7. Do you see patients/clients who used Novel Psychoactive Substances (NPS) *(please tick)*?
   [ ] Yes
   [ ] No

8. How many patients/clients using any drug did you see in the last 6 months? ……....

9. Please rate how relevant is your understanding/knowledge of NPS in relation to your work?

   *Not relevant (1) – Very relevant (5)*
   [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5

10. Did you ever use ReDNet resource/information *(please tick)*?

[ ] Yes
[ ] No

If Yes, *please tick all that apply*:

- [ ] Website
- [ ] Database/Technical folders
- [ ] SMAIL (SMS-Email system)
- [ ] Newsbites (ReDNet media summaries)
- [ ] Academic papers/journal articles/academic dissertations
- [ ] Material related to conference presentations/posters
- [ ] Short films/Art communication project
- [ ] Correspondence/communication with researchers on specific matters
- [ ] First International Conference on Novel Psychoactive Substance Conference
- [ ] Other, please specify: …….

11. How did you use this? (*Please tick all that apply)*

[ ] To inform policy
[ ] To inform practice/treatment
[ ] To educate myself/my organisation
[ ] To inform service commissioning/provision
[ ] To provide facts to others/develop resources
[ ] To provide context for my/our research/activities
[ ] For programme planning, monitoring, evaluation
[ ] For advocacy
[ ] Other, please specify: .....

12. Why did you use this? *(Please tick all that apply)*

[ ] It is up to date
[ ] It is from an authoritative source
[ ] It is reliable
[ ] It is value-free/objective
[ ] It fills/helps to fill a gap in the knowledge-base
[ ] It is the only source for the type of information I/my organisation need(s)
[ ] Other, please specify: .....

13. How relevant did you find this? (*Please tick one)*

*Not relevant (1) – Very relevant (5)*

[ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5

14. What difference(s) has this made to what you do/your organisation does, and with what results? (*Please give examples)*

[ ] Means decisions are evidence-based
[ ] Enables services/treatment to be tailored to specific needs/target groups
[ ] Makes me/my organisation think in a different way
[ ] Makes me/my organisation aware of new facts/emerging issues
[ ] Provides a base-line against which progress can be monitored, appropriate changes made
[ ] Update/revise policies, code of practice/conduct, etc.
[ ] Other, please specify: .....

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