

# New psychoactive substances: concerted efforts and common legislative answers for stemming a growing health hazard

S. ZAAMI

Department of Anatomical, Histological, Forensic and Orthopaedic Sciences, Sapienza University of Rome, Rome, Italy

**Abstract.** – **OBJECTIVE:** New psychoactive substances (NPS), are a range of drugs designed to mimic the effects of established illicit drugs, being legal at the time of their distribution in illicit markets. The review aims to shed a light on the growing threat caused by NPS, and on the dynamics and developments that have led to their spread, including the risk of new adulteration practices which can cause a serious health threat, due to their increased toxicity, e.g., through fentanyl and its analogs.

**MATERIALS AND METHODS:** An overview of statistical trends relative to NPS use has been provided, in addition to regulatory and legislative approaches in several countries and recommendations and data from International institutions: UN Office on Drugs and Crime, United Nations Commission on Narcotic Drugs, WHO, European Parliament, European Monitoring Centre for Drugs and Drug Addiction, Europol and international collaborative efforts such as the Trans European Drug Information (TEDI) project and the Spanish Energy Control.

**RESULTS:** Given the elusive nature of NPS, spontaneous pharmacovigilance reporting systems are needed to identify new trends of drug abuse. Broad-ranging legislative initiatives are needed in order to set common international standards (e.g., the European Parliament Regulation 2017/2101, with information exchange, an early warning system and risk assessment procedure for NPS) to tackle a potentially catastrophic and growing threat.

**CONCLUSIONS:** By virtue of all the complexities and hurdles that have to be overcome in the fight against NPS, and to assist national governments in their identification and reporting, supranational organizations can come to play a key role. Only through international measures, supplementing national legislative initiatives, can this multi-faceted problem be effectively addressed and information about NPS be gathered and disseminated in a timely fashion.

*Key Words:*

New psychoactive substances, Adulteration, Drug of abuse, Legislative measures.

## Introduction

New psychoactive substances (NPS) are a range of drugs that are designed, manufactured and marketed to replicate the effects of illegal established substances (e.g., cannabis, cocaine, ecstasy and LSD<sup>1</sup>). At the time of their arrival on street and web markets, such substances are mostly not scheduled under the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances. Manufacturers of these drugs deliberately develop new chemicals to replace others that have been banned. In this concern, NPS chemical structures constantly change and develop in an attempt to stay ahead of the national and international banning laws, and when a new substance is scheduled a new analog is created to restart the process of distributing a free psychotropic substance. Over the past decade, the emergence of hundreds of NPS has represented a daunting challenge for public health and drug policies on a global scale. Such drugs are relatively new to recreational drug markets, and the definition encompasses all NPS, as well as drugs that even though not newly synthesized, have recently seen a significant rise in terms of illegal use<sup>2,3</sup>. NPS may be categorized by chemical structure, psychoactive properties, biological targets, or by source (plant, synthetic, or combined<sup>4</sup>), and can be subdivided into four main categories:

- Synthetic cannabinoids – they mimic the cannabis effects and are traded under various “street names”. They show no chemical relation to delta-9-tetrahydrocannabinol, the psychoactive principle of cannabis, but they act on cannabinoid brain receptors in a similar way to that of cannabis.
- Stimulant-type drugs – they simulate the psychoactive effects of substances such as am-

phetamine, cocaine and ecstasy and include compounds such as e.g., benzylpiperazine, synthetic cathinones (e.g., mephedrone), methylphenidate and analogs, methylenedioxypropylamphetamine, 5,6-methylenedioxy-2-aminoin-dane, ethylphenidate. New benzodiazepines and tranquilisers (a.k.a., ‘Downer’/tranquiliser-type drugs), which are designed to replicate the effects of tranquilisers or anti-anxiety drugs, especially from the benzodiazepine family, including, among others, etizolam, pyrazolam and flubromazepam.

- Hallucinogenic drugs – these drugs simulate the central action of substances like lysergic acid diethylamide and include the substances of 2-C phenethylamines (2-CB, 2-CE, 2C-I), ketamine, deschloro-N-ethyl-ketamine.

### **Broad-ranging variety only adds to the problem**

NPS, sometimes incorrectly called “legal highs”, are being developed at an unprecedented rate since the beginning of the century. The two years which registered the highest number of NPS seized in the European Union have been 2014 and 2015<sup>5</sup>. In this concern, as of December 2015, a total of 643 new psychoactive substances were reported in the United Nations Office of Drugs and Crime (UNODC) Early Warning Advisory on NPS<sup>6</sup>. The emergence of 75 NPS was reported for the first time in 2015, most of them belonging to synthetic cannabinoids (which act as Synthetic Cannabinoid Receptor Agonists, 21), synthetic cathinones ( $\beta$ -keto phenethylamines and chemically similar to amphetamine and methamphetamine, 20) and phenethylamines (most of which act as either central nervous system stimulants, or as hallucinogens, 9), in addition to 21 more, that are structurally diverse and do not belong to any of the above mentioned groups<sup>7</sup>. After those two years, the yearly number of reported substances started to decrease, mainly due to the fact that banning laws imposed more severe and specific restrictions to the classes of prohibited psychotropic drugs and to the seizing action of police forces. Nevertheless, by the end of 2018, the EMCDDA was monitoring more than 730 new psychoactive substances, 55 of which were detected for the first time in Europe in 2018. These include synthetic cannabinoids, stimulants (including cathinones), hallucinogens and opioids that are designed to mimic the effects of established substances<sup>8</sup>. A

phenomenon that has to be highlighted is given by the evidence that the most recent NPS started to be targeted to a different type of consumers, thus transitioning from being substances for recreational weekend music parties and casual sexual scenes to narcotic and depressant substances aimed at chronic heroin users, namely new synthetic opioids and new benzodiazepines<sup>9-11</sup>.

### **Lawmakers and regulatory bodies strive to keep up**

The European new psychoactive substances (NPS) market has increased at a somewhat alarming rate, to such an extent that established drug control laws have struggled to keep up. Several countries have therefore devised and enacted new legal responses to this phenomenon, either based on existing laws (mostly focused on consumer or health protection or pharmaceuticals), or by passing new and innovative pieces of legislation. As of 2018, over 60 countries have implemented legal responses to control NPS, many of which resorted to the existing legislation, sometimes properly amended, while others decided to draw up and enact innovative legal instruments. Several European and non-European countries (Austria, Denmark, France, Hungary, Hong Kong, Ireland, Israel, Japan, Lithuania, Norway, the Russian Federation, Switzerland, the United Arab Emirates, the United Kingdom and the United States<sup>12</sup>), where a large number of different NPS has rapidly emerged, have adopted controls on entire substance groups of NPS using a so-called generic approach, or have introduced analogue legislation that invokes the principle of “chemical similarity” to an already controlled substance in order to control substances not explicitly mentioned in the legislation. Legislation regulating known NPS varies internationally. In Germany, a draft law was adopted by the government in May 2016, to be eventually enacted by parliament in September of the same year. Under this draft law, NPS are defined as any substance or preparation which belongs to a specified generic group definitions for synthetic cannabinoids and compounds derived from 2-phenylethylamine. It should be noted however that substances that are already listed in the Narcotics Act or Medicines Act have been exempted. Based on expert advice, the German Health Ministry has the authority to amend or update such definitions. Manufacturing, trading, importing, possessing and offering NPS is unlaw-

ful under the legislation; law enforcement agencies are entitled to confiscate and dispose of such substances, by virtue of their authority to protect life and health. Customs officials may confiscate substances that they have good reason to believe are potentially harmful NPS. As for offences arising from smuggling and supply, penalties, up to 10 years in prison are set in the law. Trade for recognized commercial, industrial or scientific uses is excluded<sup>13</sup>. In Romania, targeted NPS legislation was enacted in 2011, according to which any product likely to provoke psychoactive effects similar to those caused by substances controlled under drug law requires a specific permit to be legally sold. Such effects are characterized as liable to bring about ‘changes in functions and mental processes and behaviour’, or ‘causing addiction’; it is worth noting, however, that no precise reference is made to ‘harmful’ substances. Unlawfully supplying NPS and their advertisement are punishable by detention and custodial sentences, whereas possession for personal use is not<sup>14</sup>. In Finland, new legislation was enacted, coming into force on 20<sup>th</sup> December 2014. According to the new set of norms, NPS are comprised in the Finnish Narcotics Act and listed in the government regulation on the consumer market of psychoactive substances. It is noteworthy that for a specific NPS to be banned in Finland, it should be included that regulation. In addition, the Finnish criminal statutes were amended so as to provide for a general provision of subsidiary application, designed to effectively outlaw NPS manufacturing, import, storage and possession for sale (Chapter 44, Section 5a). Such a provision applies only where the felony is not more severely punished by another criminal law provision. Since most NPS-related criminal offences have to do with importing, which is prosecuted and punished as smuggling (carrying harsher penalties under Chapter 46, Section 4), the provision has a limited range of application<sup>15</sup>. The Austrian Parliament enacted in 2011, the New Psychoactive Substances Act (*Neue Psychoaktive Substanzen Gesetz*), a Federal Act on the Protection against health hazards arising from new psychoactive substances. The law characterizes a ‘new psychoactive substance’ as “a substance or preparation which has the capacity to cause a psychoactive effect in the human body when consumed...” (Article 1). The piece of legislation vests in the Federal Minister of Health the authority to define individual NPS or classes of chemical substances through regulation for control purposes, whenever this proves

necessary in order to prevent their distribution and avoid ensuing health hazards. Two conditions must be fulfilled for any substance to fall within that definition: (1): it can be assumed that they will be distributed for the purpose of being misused by certain groups of individuals for its effect...” and (2): “according to the current state of scientific knowledge and experience, they may pose a health hazard to the consumers or such hazard cannot be ruled out when applied<sup>16</sup>”. France, in the context of the governmental plan set up to tackle the spread of drugs and abusive behaviour, established in March 2014 a specialized working group made up of representatives of the Ministries of the Interior, Justice, Economy and Health within named MILDECA (*Mission interministérielle de lutte contre les drogues et les conduites addictives*: Interministerial Mission for the Fight against Drugs and Addictive Behaviour<sup>17</sup>). Such a group has been tasked with exploring and assessing all legal instruments that could be fit to identify NPS that are potentially harmful to public health<sup>18</sup>. NPS in France are regularly subjected to assessment and listed as narcotics. In that regard, seven families of synthetic cannabinoids were defined as such by a decree of the Minister for Health, on 19<sup>th</sup> May 2015. Moreover, prosecutors strive to offset the existing legal vacuum by indicting, whenever and to the extent possible, traffickers for criminal association (*association de malfaiteurs*). Besides, if dealers or distributors purport NPS as bearing the same characteristics (and eliciting the same effects) as an illegal drug, they can be charged with the crime of “incitement to use or traffick illegal narcotics” (*provocation à l’usage ou au trafic de produits stupéfiants*) through the Public Health Code (Article L.3421-4). That criminal offence is impactful in terms of online peddling<sup>19</sup>. In France, just over 300 substances in total were recorded in France (as opposed to approximately 650 in Europe), comprising 11 chemical classes. The number of new NPS detected appears to have dwindled in recent years (from 53 in 2015 to 44 in 2016, and 15 in 2017). A mere 3 new compounds were detected in the first semester of 2018. Apparently, such a decrease is unrelated to customs and drug enforcement agencies, which on the contrary have reported an increasing number of seizures each year: nearly 900 in 2015, over 2,000 in 2017<sup>20</sup>. In the UK distribution and sale of NPS are illegal, whereas possession is not a criminal offence. In the UK, the 2016 Psychoactive Substances Bill<sup>21</sup>, based on recommendations from an

NPS Review Expert Panel, banned trading but not possession of all current and future NPS, in an attempt to stem the rapid proliferation of these compounds. The new legislation has been at the receiving end of criticism, and has been labeled legally flawed<sup>22</sup>, especially in terms of establishing a total ban and associating penalties with substances whose harmfulness, in many cases, has not yet been established<sup>23</sup>. Ireland has tackled NPS through a general prohibition on the distribution of non-controlled substances. The 2010 Irish Republic's Criminal Justice (Psychoactive Substances) Act was passed on 23<sup>rd</sup> August 2010, as a reaction to the proliferation of retail premises selling various NPS. The Act makes it illegal under criminal law statutes to advertise, supply, import, export or sell a psychoactive substance, while being aware that it is meant for human consumption, and is applicable to substances that are not explicitly prohibited under the Misuse of Drugs Acts. The Act does not contain any offence for possession for personal use of these substances nor does it have a production offence: it is targeted at peddlers rather than users. As a result of the new legislation, the head shop trade, selling in the past the so called "legal highs" namely NPS not yet under banning legislation, in Ireland has almost vanished, with very few such outlets still open for business, while being continuously monitored by the authorities<sup>24</sup>. Further legislation was also passed in Ireland in May 2011 under the Misuse of Drugs Act 1977 and 1984, controlling 200 psychoactive substances among which benzylpiperazine derivatives, synthetic cannabinoids, mephedrone, methylone and related cathinones, ketamine, Tapentadol, GBL and 1, 4 BD. The proliferation of legal headshops in Ireland was so fast before the law that such outlets were opening at approximately one per week<sup>25, 26</sup>. In the United States, the Federal Government has opted for what could be characterized as an "analogue approach": substances are controlled based on their "chemical similarity" to other drugs that are already controlled. Under the Controlled Substance Analogue Enforcement Act 1986<sup>27</sup>, it is unlawful to peddle or provide a substance for human consumption that is listed as a controlled substance analogue. A suspect is held criminally liable for drug-trafficking under the 1986 Act if it is proven that the substance was meant for human consumption and: (1) that substance's chemical structure is substantially similar to a controlled substance's and either (2) that the depressant, hallucinogenic, or stimulant effect on the central

nervous system is remarkably similar to or greater than that caused by a controlled substance or (3) that the defendant represented the substance as having a similar or greater effect on the central nervous systems as a controlled substance. Prosecutions under this legislation have generally been very resource intensive: judges and juries often hear differing expert evidence, which they are supposed to thoroughly assess in order to determine whether it is warranted for a given substance to be treated as a controlled substance analogue<sup>28</sup>. The United States Federal Government has recently taken up a "neurochemical approach", aimed at controlling substances on the basis of their effects on the user's brain. Those provisions are codified in the Synthetic Drug Abuse Prevention Act 2012<sup>29</sup>, which has effectively classified several synthetic cannabinoids (or cannabimimetic agents) within the scope of the 1970 Controlled Substances Act. In New Zealand, the Psychoactive Substances Bill was turned into law by Parliament in July 2013 by 119 votes to one, thus becoming the Psychoactive Substances Act<sup>30</sup>, in an effort to cope with the unregulated use of NPS. Under the legislation, manufacturers and providers of any psychoactive substance including energy pills, party pills, and herbal products are legally bound to provide scientific evidence proving that their product is 'low-risk' to the consumer. Apparently, a transition has been made by the government of New Zealand: from outright prohibition to a new regulatory framework akin to medicines regulations. The manufactures/sellers/importers of NPS are required to have their product either green-lighted or rejected by the government based on the company's pre-clinical and clinical data. That arguably constitutes a somewhat innovative approach to the legal high problem, with some analysts hailing the new law as "good example of the start of evidence-based policy"<sup>31, 32</sup>.

Finally, in Italy, since July 2007, by separate updated decrees of the Ministry of Health, many new psychoactive substances, have been included in the Presidential Decree n. 309/90<sup>33</sup>, and subsequent amendments and additions which rule the banning of psychotropic substances. NPS have been progressively introduced as singles substances and only in case of synthetic cannabinoids and synthetic cathinones, analogs have been indicated with a general chemical structure (e.g., for synthetic cathinones: analogs of 2-amine-1-phenyl-1-propanone, for one or more substitution on the aromatic ring and/or on nitrogen and or

on terminal carbon and for synthetic cannabinoids: structural analogs of indole 3-carboxamide, indazole 3 carboxamide, 1 naphthoylindole, phenylacetylindole and benzoylindole). Generally speaking, NPS are not controlled under the International Drug Control Conventions, hence their legal status can greatly differ from country to country. At the international level, up to March 2018, the United Nations Commission on Narcotic Drugs decided to place 39 NPS under international control<sup>34</sup>. These control measures need to be implemented into the national legal framework of each country. In 2014, the Court of Justice of the European Union ruled that substances are not medicinal products if they do not have beneficial effects on human health, thus restricting the use of such laws for NPS control. Several recent legislative responses have undoubtedly been successful in reducing availability and sales of these substances in some settings (e.g., “legal highs” and research chemicals openly traded in the street and online), new challenges have come to the fore. This includes monitoring a growing number of highly potent substances – including 179 synthetic cannabinoid receptor agonists and 28 fentanyl – that can pose a high risk of life-threatening poisoning to users and can cause explosive outbreaks<sup>35</sup>. The European Union has recently decided to put in place a faster process for regulating new psychoactive substances at the European level. Regulation (EU) 2017/2101 of the European Parliament and of the Council, amending Regulation (EC) No 1920/2006 with reference to information exchange on new psychoactive substances came into force on 23<sup>rd</sup> November 2018, including an early warning system and risk assessment procedure<sup>36</sup>. It is worth noting that NPS do not typically come with a recommended dosage printed on the label. They are unregulated and untested, which only adds to their potential harmfulness. Given that the chemicals in these drugs are constantly changing to try to stay ahead of the law, it is possible for users to receive very different products, varying from batch to batch, although the packaging and name may read the same. At this point, toxicity and health risks are unpredictable. Indeed, there is limited information available about NPS short and long-term effects<sup>37,38</sup>. However, synthetic cannabis has been found to have more serious side-effects than cannabis<sup>39</sup>; cardiovascular, gastrointestinal, neurological, kidney, metabolic, ophthalmologic, pulmonary and psychoactive adverse side-effects have been observed, including addiction and withdrawal.

Several cases of synthetic cannabinoids ingestion have been linked to liver failure as well<sup>40</sup>. The use of NPS has often been associated with health problems, with side effects ranging from agitation to seizures, hypertension, tachycardia, aggression, acute psychosis and potential addiction<sup>41,42</sup>. The novel nature of NPS, the degree of ambiguity surrounding their legal status, their ability to evade toxicological tests, their prompt adaptation to regulatory and legal efforts, the global Internet marketing, and a low degree of public awareness as to their harmful health effects are among the key drivers of this twenty-first century phenomenon. Effective responses need to be produced through multi-disciplinary research efforts in the areas of biology, epidemiology, prevention, and web analytics, in a realm liable to overwhelm national drug control policies, as well as international conventions.

### **NPS adulterants: a potentially deadly challenge**

The use of NPS as adulterants has not yet gained much attention in terms of specific research. European drug testing services in the type of adulterants detected several NPS types in ecstasy tablets (sold as such) or purportedly MDMA powders. According to an analysis of some of the most frequently detected NPS in ecstasy across five European drug testing services, several substances appear to have sort of a geographic link to certain countries: 4-methylethcathinone (4-MEC) was marketed in Switzerland, Spain and Austria, whereas 4-Fluoroamphetamine (4-FA), 4-APB, 5-APB, 6-APB, PMMA and PMA and its analogues only seemed to show up in the Netherlands<sup>43</sup>. Drug-checking services in Portugal reported in 2014 the presence of NPS as adulterants in lysergic acid diethylamide (LSD), another common party drug: out of 245 samples of LSD analyzed, 24.1% did not contain LSD at all, but did contain another psychoactive substance, 11.4% of which were found to be 2,5-dimethoxyamphetamine derivatives and 9.8% N-benzyl-2,5-dimethoxyphenethylamine derivatives<sup>44</sup>. A net increase has been registered over time in terms of the number of substances used as adulterants of ecstasy as well, according to findings released by the Trans European Drug Information (TEDI) project, in which Spain, Switzerland, Belgium, Austria, Portugal, and the Netherlands have partaken, providing data from their respec-

tive drug testing systems<sup>45</sup>. According to the Spanish project Energy Control, which collects and analyzes drug samples throughout Spain, the NPS adulterant most frequently observed was 2-(4-bromo-2,5-dimethoxyphenyl)ethanamine (2C-B) followed by 1-(4-fluorophenyl)propan-2-amine (4-FA)<sup>46</sup>. Fentanyl, a potent, synthetic and highly lipophilic, opioid acting mostly on  $\mu$ -opioid receptors<sup>47</sup> first synthesized by Janssen Pharmaceutica in the 1960s<sup>48</sup>, has been found to play a major role as a heroine adulterant as well. Studies have shown that since 2001, deaths related to heroin overdose have risen six-fold in the United States<sup>49</sup>; such an increase cannot be accounted for by the rising user population. Heroin use rose 63%, from 2002 to 2013 and in 2015 an estimated 833,000 people had used heroin in the last year<sup>50</sup>. Reports of fentanyl and its analogs (such as Crotonylfentanyl<sup>51</sup> and Valeryl fentanyl<sup>52</sup>), often concealed in or sold as heroin, have also increased sharply<sup>53</sup>. Fentanyl, fentanyl analogs and other novel synthetic opioids are all full agonists of varying potencies at the  $\mu$ -opioid receptor, leading to typical clinical effects of miosis and respiratory and central nervous system depression. Due to their high affinity for  $\mu$ -opioid receptors, larger doses of naloxone are required to reverse the effects than commonly used<sup>54</sup>. Fentanyl is legally prescribed and used as a synthetic opioid pain reliever, approved for treating severe pain, typically advanced cancer pain, for which it is prescribed in the form of transdermal patches or lozenges and can be diverted for abuse. Its potency is 50-100 higher than that of morphine; since fentanyl and heroin are approximately 100 and 2.5 times the potency of morphine, respectively, fentanyl is roughly 40 times stronger than heroin per mg<sup>55</sup>. Overdose outbreaks in the US have long been ascribed to fentanyl and its analogs<sup>56,57</sup>. According to data from the National Forensic Laboratory Information System, confiscations, or seizures, of fentanyl have risen nearly 7 fold from 2012 to 2014. 4,585 fentanyl confiscations occurred in 2014, which suggests that the sharp rise in fentanyl-related deaths may be due to increased availability of illegally made, non-pharmaceutical fentanyl, and not prescribed fentanyl<sup>58</sup>. Although toxicological testing for fentanyl has proven somewhat uneven in terms of outcomes, an analysis of 27 states has shown an increase in fatalities associated with fentanyl in 2014 over 2013 levels: from 392 to 1400<sup>59</sup>. Hence, it is of utmost importance to develop and validate analytical methods for the determination of NPS both in tra-

ditional and alternative matrices, which would go a long way towards clarifying drug metabolism and ascribing consumption to clinical outcomes and ensuing possible intoxication symptoms<sup>60</sup>. As supply has gone up, fentanyl overdose-related casualties have doubled from 2012 to 2014<sup>61</sup>. The substantial scope of the structural risk increase is reflected in the volume of seized fentanyl: data from the White House Office of National Drug Control Policy (ONDCP) show that 668 kg of fentanyl powder, apparently smuggled from China, were seized in 2016, which accounts for a 426% increase from the amount seized in 2015<sup>62</sup>. Even given conservative estimates of 5% purity and a high 1:4 seizure to importation ratio, it is safe to assume that at least 134 kg of pure fentanyl entered the US in 2016. That in turn would represent 134 to 536 million replacement doses, i.e., about one dose a day for the estimated million heroin users in the US, based on a 0.25 to 1.0 mg estimate as a replacement dose for a single dose of heroin<sup>63</sup>. Suppliers have been found to use fentanyl to make up for heroin shortages and to heighten overall opioid potency<sup>64-66</sup>. As pointed out by the United States Drug Enforcement Agency, although it is sometimes diverted from pharmaceutical sources, most recent cases of fentanyl-related harm, overdose, and death in the U.S. are linked to illegally made fentanyl, manufactured and smuggled from Mexico and China<sup>67</sup>. Similar trends have been observed in European markets<sup>68</sup>.<sup>69</sup> Reports from the Swedish Police show that fentanyl analogues were introduced into the illegal drug market in Sweden in 2014; since then, similar seizures have become increasingly common in the country. During 2014, a total of 11 seizures of fentanyl analogues were executed by the Swedish customs and the police; in 2016-2017, however, the number had risen to roughly 200 seizures per year. Before that, from 2006 to 2015, the original fentanyl molecule was predominant and was detected in a total of 227 seizures, which have been analysed by the National Forensic Centre (NFC). 80 per cent of these seizures consisted of fentanyl patches, and as described earlier, they appear on the illegal market through diversions from legal sources<sup>70</sup>.

### **Economic and social sea-change may play into the hands of traffickers**

Fentanyl and other synthetic opioids are likely to become mainstays and recurrent aspects of

the heroin supply, even to the extent of becoming the “new norm”, not unlike the role of levamisole in the cocaine supply: an ever-spreading adulterant designed to heighten the stimulant effect and which has come to be sort of a normalized aspect of illicit cocaine abuse<sup>71</sup>. A further decline in illicit opium production may be brought about by economic and civil growth and development in source countries. While there used to be four sources of heroin competing for retail US markets, it is now down to two, with the oligopolistic trade of heroin manufactured and smuggled from Mexico and Colombia potentially turning into a monopolistic trade of opioids, including fentanyl, solely supplied from Mexico. It is also worth noting how the forces of globalization and neoliberal economic policies have come to play a prominent role in shaping such dynamics, leading to ever-growing flows of licit and illicit goods while, at the same time, inhibiting or greatly hampering cross-border drug trafficking<sup>72</sup>.

As for NPS themselves, they have become a global phenomenon: 119 countries and territories from all world regions have reportedly had one or more NPS-related incident. A total of 888 substances have been reported to the UNODC Early Warning Advisory (EWA) on NPS as of December 2018, by Governments, laboratories and partner organizations. NPS available on the market have similar effects as substances under international control such as cannabis, cocaine, heroin, LSD, MDMA (ecstasy) or methamphetamine. Looking at the effects of NPS that have been reported until December 2018, the majority are stimulants, followed by synthetic cannabinoid receptor agonists and classic hallucinogens.

It seems safe to say that the phenomenon of adulteration has undergone a radical change in the 21<sup>st</sup> century, in lockstep with the rise of NPS, and that has given rise to previously unheard-of health hazards. Furthermore, it is noteworthy that new psychoactive substances can themselves be subject to “cutting”, or adulteration, which adds to the risk of potentially deadly toxicity. A telling instance of such a trend is that of GHB or Gamma Hydroxybutyrate (C<sub>4</sub>H<sub>8</sub>O<sub>3</sub>), a central nervous system depressant that is illegally traded as a “club drug”, a “date rape” drug or a “chemsex” drug. GHB is also a naturally-occurring metabolite of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) found in the brain. Nonetheless, the naturally-occurring metabolite GHB is present in much lower concentrations in the brain than those levels found when the drug is abused<sup>73</sup>.

GHB, or its prodrug Gamma-butyrolactone (GBL), often used as an alternative<sup>74</sup>, is abused by teens and young adults at parties and rave parties followed by sexual intercourse. Two instances of GHB adulteration by sildenafil, a sexual enhancing drug, have recently been found in individuals who had consumed the adulterated drug for the purpose of enhancing its sexual effects, but eventually ended up facing severe intoxication<sup>75</sup>.

### **Conclusions: legislative harmonizing will go a long way towards providing new effective standards**

Many European Union Member States and the international community, in an effort to safeguard public health, have striven to devise a wide range of legislative responses to grapple with the new the dynamics of the NPS market; the issue appears to be extremely complex and multifaceted, especially in light of their rapid rise and attempts by NPS manufacturers and traffickers to circumvent legislation, and a dearth of scientific evidence and data that would allow for a thorough assessment of the NPS hazard. By virtue of all the complexities and hurdles that have to be overcome in the fight against NPS, and to assist national governments in the identification and reporting of NPS, supranational organization can come to play a key role. To that end, the United Nations Office on Drugs and Crime (UNDOC) established the Early Warning Advisory (EWA) on NPS, which is meant to serve as a valuable monitoring tool and knowledge hub, gathering organizing and presenting relevant information on NPS trends, hazards, national legislative initiatives and response, in addition to technical standards for law- and policy-makers, laboratories and law enforcement agencies. Moreover, the UNODC has laid out a set of manuals pertaining to the identification and analysis of fentanyl and its analogues, piperazines, synthetic cathinones and synthetic cannabinoids. Such indications are valuable in enhancing and fine-tuning the forensic capabilities of national drug laboratories<sup>76</sup>. Selected chemical reference standards are also distributed to forensic laboratories as part of the UNODC International Quality Assurance Program. In addition, training and awareness raising workshops for laboratories and law enforcement are provided<sup>77</sup>. As mentioned before, the number and type of NPS that have been identified as well as their patterns of emergence greatly vary among nations. In an effort to live up

to that challenge, countries have adopted a broad range of legal measures devised and laid out in order to control NPS. That approach clearly reflects the diversity of the problem as well as the differences that exist in legal and policy frameworks and priorities. Despite that diversity at the national level, the global organization of the NPS market is a common feature of the phenomena. The international drug control system serves as a common, shared frame of reference in order to devise and develop an international response to the problem. One of the crucial responsibilities will be the identification of the most widespread, noxious and persistent NPS, for which an international tackling effort may be needed. Only through international measures, supplementing national legislative initiatives, can this multi-faceted problem be effectively addressed and information about NPS be gathered and disseminated in a timely fashion<sup>78</sup>. The number of NPS unremittingly grows, and such a growth calls for a thorough understanding of such substances, the chemical profiles and complexities in addition to reliable and updated spectral databases. Institutions such as the EWS of the EMCDDA, which are focused on collecting spectral data (nuclear magnetic resonance, GC/MS, infrared) relative to such compounds from all over the world<sup>79</sup>. Crucial input for the EWS database is delivered by the different European forensic institutes and also customs laboratories, which provide the majority of the information.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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