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Legal responses to novel psychoactive substances implemented by ten European countries: An analysis from legal epidemiology ☆

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ABSTRACT

Introduction: Novel psychoactive substances (NPS) continue to pose challenges to law enforcement authorities, public health officers and policymakers as suppliers continuously adapt to control measures, thus remaining highly dynamic in introducing unpredictable and potentially toxic new substances into the drug market. Using a legal epidemiology approach, the aim of this study was to assess the effectiveness of NPS legal measures in preventing NPS use (legal prevention and control), as well as NPS-related intoxications and deaths (legal aetiology).
Methods: We conducted a comparative analysis of legal instruments adopted at national level as a response to NPS by ten European countries between 2008 and 2019. The data collection process encompassed (i) a scoping review aimed at mapping out the current state of NPS-related legal measures, and (ii) the collection of nationally produced health data on three NPS-related health indicators (prevalence of use, acute intoxications and deaths).
Results: Based on both the legal approaches and the regulatory model adopted by countries a five-elements typology was elaborated. Implemented measures – particularly individual listing – may be relatively effective in preventing NPS use, at least in the short-term. However, they are also very likely to affect the purity and potency of substances, which may have an indirect negative impact on users' health. In fact, an increase in NPS-related poisoning episodes and deaths has been observed in most of the countries having introduced control measures, regardless the regulatory model adopted.
Conclusions: Policy responses to NPS implemented across Europe have not been markedly effective in deterring their use nor in preventing health harms. Therefore, there is a need for innovative initiatives to regulate drug markets that go beyond law enforcement. Considering scientific evidence on underlying factors leading to the use of psychoactive substances may better inform policy responses to address users' motivations while reducing their exposure to health risks.

1. Introduction

Novel psychoactive substances (NPS) are defined as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat" (UNODC 2013a). NPS can be analogues of controlled drugs or newly synthesized chemicals intended to mimic the psychoactive effects of already known illicit substances. Although some NPS are not necessarily new inventions but substances that have recently become available, their appearance in the international drug market continues to pose challenges to law enforcement authorities, public health officers and policymakers as suppliers and distributors continuously adapt to bans and control measures adopted, thus remaining highly dynamic in providing unpredictable and potentially toxic new substances into the drug market (Seddon, 2014; Bicknell et al., 2017; Peacock et al., 2019). As a result, several policy responses such as the implementation of risk assessment procedures and monitoring systems along with control measures have been adopted at international, supranational and national levels across Europe to reduce deleterious effects of NPS use on population's

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health (EMCCDA 2006; UNODC 2021 November 2021; EMCDDA 2004; EMCDDA 2009).

Further to a previous exploratory policy analysis conducted in 2018 (Neicun et al., 2018), this study focuses on the effect that legal measures adopted by a selection of European countries have had in terms of deterring the use of NPS amongst general population, while preventing their harmful effects on users' health. Using a legal epidemiology approach (Burris, 2017; Burris et al., 2020; Ramanathan et al., 2017), the aim of this study was to assess the effectiveness of NPS-related legal measures in preventing (i) NPS use (legal prevention and control), (ii) NPS-related acute poisonings and (iii) NPS-related fatal overdoses (legal aetiology). Commonly used health indicators such as drug treatment demand were not included in the analysis due to the lack of NPS-specific data for all the countries under study. Study findings are intended to support evidence-based policymaking in the drug use field thus improving public policy responses to health and social harms related to NPS use.

2. Conceptual framework

Law and public policy are significant factors in public health as they introduce changes in population environments and socioeconomic conditions, while they may promote healthier lifestyles through behavioural change. Well-designed laws may have a crucial influence on social determinants of health by establishing rules and frameworks that shape social and economic interactions in a safe and healthy way. Nevertheless, when poorly designed, implemented, or enforced, regulatory interventions could also involve unexpected negative effects on health and wellbeing, harming some already marginalised populations while reinforcing stigma and discrimination (Pepin et al., 2017; Frieden, 2010; Gostin et al., 2019). Considering the importance of law as a tool for public health, scientific research started to focus its work on the impact of specific legal interventions on health during the last decades. The incorporation of scientific standards to the study of how laws and legal practices affecting public health has marked the emergence of a Public Health Law Research (PHLR) framework. As defined by Burries et al. PHLR is "the scientific study of the relation of law and legal practices to population health. This includes both direct relationships between law and health, and relationships mediated through the effects of law on health behaviours and other processes and structures that affect population health" (Burris et al., 2010). PHLR is therefore focused on whether law can be empirically shown to have an impact on the population health. It uses systematic methods to collect and analyse data in order to test (to prove or disapprove) hypothesis and thus answering research questions (Burris et al., 2010).

As the study of social and environmental factors related to health, the study of the effects of legal interventions on health has found on the PHLR framework a scientific approach providing crucial tools for the development, implementation and assessment of health-related law and policy (Burris et al., 2016). PHLR encompasses both "interventional public health law" – or laws that were intended to have a direct influence on health outcomes or mediators – and "incidental public health law" – or laws not intended to influence health that can have powerful incidental effects on it (Burris et al., 2020, 2010). Thus, PHLR evaluates the effectiveness of law as the tool used to implement or facilitate a public health intervention.

Furthermore, understooding law as a social practice embedded in institutions and implemented by agents, it can also be considered as part of the social environment whose influence on health is the focus of social epidemiology (Burris et al., 2010). Thus, legal epidemiology has emerged as a transdisciplinary approach that provides theoretical constructs and standard methodological tools allowing for a comprehensive study of law's intended (legal prevention and control) and unintended (legal aetiology) effects on population health. Legal epidemiology is therefore defined as "the scientific study of law as a factor in the cause, distribution, and prevention of disease in a population" (Burris et al., 2016).

Within this conceptual framework, legal responses to the appearance of NPS in the European drug market – including EU Directives, national drugs legislation and statutory and regulatory instruments – are intended to restrict both their supply (import/export; production/manufacture; sale) and demand (consumption/possession). Thus, legal responses to NPS are considered as interventional laws as they are intended to directly influence drug users' health outcomes by preventing the use, acute intoxication and mortality associated with potentially dangerous novel psychoactive substances (Martini et al., 2016). Therefore, this study focuses on the effectiveness of NPS-related laws and regulations as a public health intervention aimed at tackling the health harms associated with their use. To this purpose, effectiveness is understood as the capacity to reduce both NPS prevalence of use and potential harmful effects on users' health. Hence, the study may be defined as an interventional legal epidemiology study that analyses the state of law and regulations surrounding the availability and supply of NPS, while assessing their intended and unintended effect on the abovementioned specific NPS-related health outcomes.

Although there is no general assumption of causal link between laws/regulations and NPS use, intoxication and mortality, there is an assumption of association between control measures adopted to reduce the availability of substances that pose or may pose a risk to population health – as it is stated in the definition of NPS given by enacted legal instruments (see Appendix 1) and their actual consumption by population which may have deleterious effects on users's health. Even though this theoretical perspective does not consider a variety of confounding and/or mediating factors intervening in drug use behaviours, it may still be worthwhile to examine the actual impact of drug control measures on drug users' exposure to health risks.

3. Methods

The cross-national comparative analysis carried out for the purpose of this study was based on a description of legal instruments adopted as a response to the appearance of NPS by ten European countries [Belgium, Czech Republic, France, Germany, Ireland, the Netherlands, Poland, Portugal, and Great Britain (England & Wales, Scotland)] between 2008 and 2019. The selection of countries was guided by the availability of data on three NPS-related health indicators: (i) prevalence of use, (ii) acute intoxication/poisoning, and (iii) mortality. The use of a convenience sample of countries that report data on health indicators of NPS consumption and associated harms assumes that the mere production of NPS-related health indicators reflects the magnitude of the public health concern those substances represent for some countries. In that regard, a convenience sample of countries is considered to provide a comprehensive overview of the NPS situation across Europe.

Since there is no European cross-national data source on NPS legal instruments, governmental websites formed the primary source of data collection.

3.1. Data sources

The data collection process encompassed two main components. The first component was based on a scoping review aimed at mapping out the current state of NPS-related legal measures adopted at national level in the countries under study. The second component consisted of a collection of health data produced by countries on three indicators on: (i) prevalence of NPS use, (ii) NPS-related acute intoxication/poisoning episodes and (iii) NPS-related deaths.

As for the first component, the methodological choice was based on the exploratory and descriptive nature of scoping reviews, as well as on the opportunity they offer to identify and synthesize data in a rigorous manner to describe key concepts in a given field (Peters et al., 2021; Grimshaw, 2020). Additionally, as scoping reviews can include all

types of literature, they are particularly useful in mapping non-research data sources such as project reports, government and policy documents (Goodwin et al., 2008).

Data sources included NPS-related domestic laws and regulations, policy documents and policy evaluation reports produced by countries between 2010 and 2021. National and European reports on drug-related issues (Country Drug Reports to the European Monitoring Centre for Drugs and Drug Addiction - EMCDDA, Reitox National Focal Points Reports to EMCDDA) were also used as source of legal and policy data.

3.2. Data collection

The first step in the data collection was to identify legislation focussing on novel psychoactive substances through targeted searches. Legal and policy documents were directly extracted from primary governmental sources from the ten countries under study. As this study represents an updated version of previous research on NPS-related policy previously conducted by the authors, the data collection process encompassed a combination of data already collected (Czech Republic, The Netherlands, Poland, Portugal, and Great Britain) and the collection of data for countries newly included in the study (Belgium, France, Germany and Ireland). Additionally, a search of relevant documents in the free database Google scholar was conducted. Search terms used to this purpose included: “novel/new psychoactive substances”; “drug policy”; “law”; “policy”; and “regulation”. Additionally, combinations of terms were used: “novel/new psychoactive substances & drug policy”; “novel/new psychoactive substances & law”; “novel/new psychoactive substances & policy”; “novel/new psychoactive substances & regulation”.

The scoping review yielded a corpus of main policy documents that was composed of a combination of a snow-ball sampling and a targeted search query of legal instruments, policy evaluation reports and academic articles in the free scientific database Google Scholar. The data collection took place between March and September 2021. The main reasons of exclusion were differences in scope such as focus on classic illicit drugs, and differences in time frame.

Regarding the second component, data on prevalence of use amongst adult population has progressively been produced by countries through national drug surveys either in an aggregated (encompassing different NPS as whole group of drugs) or in a disaggregated form (individual substances or drug families). Surveillance data on acute intoxication/poisoning episodes, and deaths related to the consumption of NPS is collected by countries through regular administrative tools, as well as toxicology and forensic registers, then disclosed namely via national drug reports and/or specific surveillance reports elaborated by national statistics offices, specialised health agencies, toxicology and forensic centres, but also through peer-reviewed articles (see Appendix 2 for in-depth information on data sources). As the study’s data encompasses laws, policy documents, official statistics and surveillance data produced by selected countries, no ethics approval was required to conduct the study. The findings were reported using the PRISMA framework (Moher et al., 2010).

3.3. Eligibility criteria

The general inclusion criteria used in the scoping review related to (i) the type of document (NPS-related domestic laws and regulations; policy documents and policy evaluation reports; national and European reports on drug-related issues), (ii) its source (documents drafted by a governmental body or under the aegis of it), and (iii) the publication date (documents issued between 2010 and 2021). Documents published mainly in English, but also in French and Portuguese were included in the analysis. General drug laws were always included regardless of publication date and no limitation was set on language. Documents in languages other than English, French and Portuguese (i.e., Dutch, Polish and Czech) were translated into English with the assistance of online translation services such as DeepL and Google translator. Data collection and analysis was conducted by the main author, with the supervision and validation of co-authors.

3.4. Data analysis

Data analysis was guided by the Public Health Law Research (PHLR) framework which is focused on the scientific study of law and regulatory practices as contributing factors to population’s health and wellbeing. Thus, data collection and analysis were aimed at describing and explaining the relationship between NPS-related laws/legal interventions and public health concerns, highlighting the way in which those legal interventions can be empirically shown to have an impact on three specific NPS-related health outcomes (prevalence of use, acute intoxication/poisoning episodes, and mortality).

As a starting point of the data analysis process, we conducted content analysis using a coding scheme that allowed the identification of main features of the legal responses and officially adopted texts intended to define the course of legal and enforcement action regarding NPS. The aim of this content analysis was to identify variations in the characteristics of the legal responses adopted across jurisdictions under study. Main features of NPS-related legal interventions were classified according to both the legislative approach (amendments to general drug law or NPS-specific law or regulation) and the regulatory model implemented (individual listing of new substances, generic control of groups of new substances based on their chemical structure, prohibition of any new psychoactive substance). Moreover, the analysis included additional legal measures adopted to counter the availability and supply of NPS such as closure of specialised stores (so-called head shops or smart shops) that sell products related to cannabis and tobacco consumption along with various drug paraphernalia (pipes, bongs, vaporizers, rolling papers, trays, grinders, etc.), in which NPS were usually sold.

Subsequently, we performed a descriptive analysis of the three specific NPS-related health outcomes selected for the study using official statistics on NPS prevalence of use (population-based surveys), NPS-related acute intoxication/poisoning episodes (administrative data on either admission to Accident & Emergency departments or information inquiries addressed to poison centres associated with the in-take of NPS), as well as NPS-related mortality (toxicology and forensic surveillance data).

Finally, following the legal epidemiology approach, legal responses to NPS were assessed upon their impact on reducing both NPS prevalence of use (legal prevention and control) and their potential harmful effects on users’ health (legal aetiology). Results from this three-level analysis are presented in Section 4.

4. Results

We identified three hundred and fifty-three (353) sources of data through targeted and databases searches and 25 through snow-ball sampling. One hundred and thirteen (113) sources were ultimately included in the study: 29 NPS-related domestic legal instruments (laws and regulations); 6 policy documents and policy evaluation reports; 37 national reports on drug-related issues; 36 reports on drug-related issues published by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA); 5 peer-reviewed articles on drug policy analysis. The selection process is illustrated in Fig. 1.

The effects of legal interventions on NPS prevalence of use and its deleterious effects on health were analysed following a typology approach based on the nature of legislative approaches (amendments to general drug law or introduction of NPS-specific laws) and the regulatory model implemented (individual listing, generic model, blanket ban). Five combinations – or typologies – were identified across the ten countries under study.

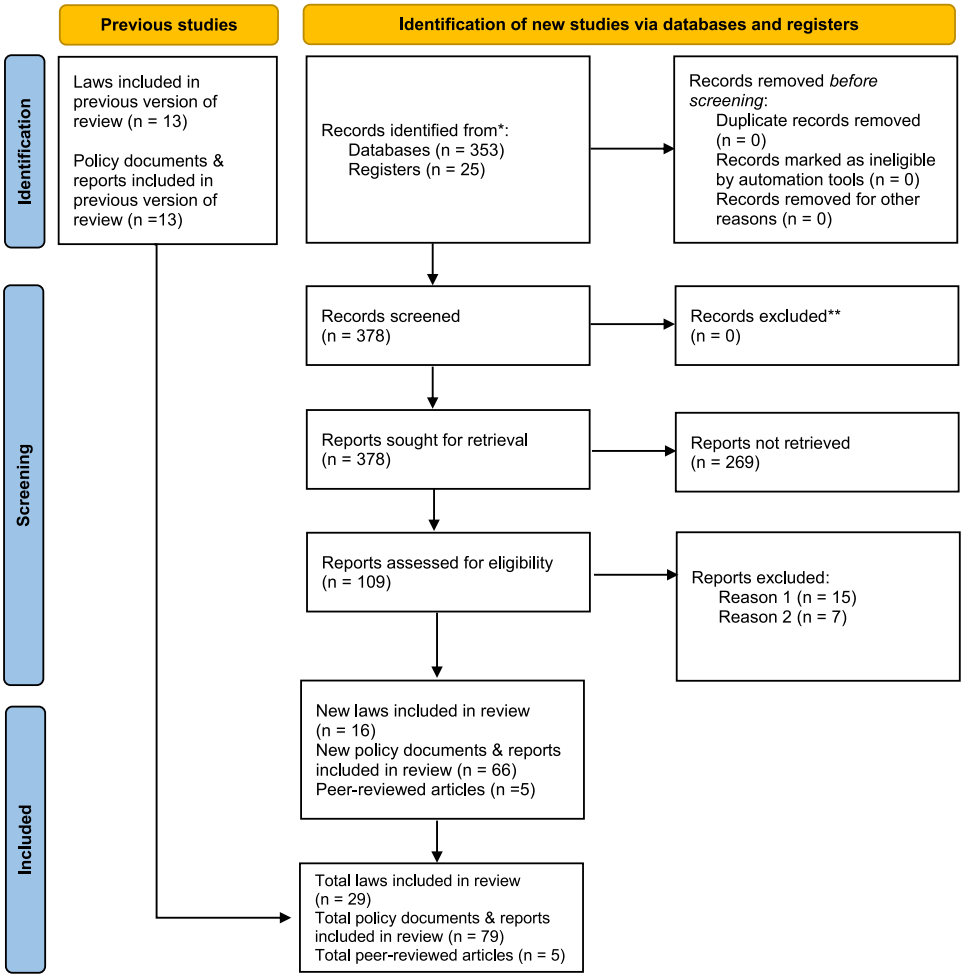

Fig. 1. PRISMA 2020 flow diagram for updated systematic reviews.

4.1. General law—Individual listing

In The Netherlands, the response to the threats to public health posed by NPS consists of the introduction of subsequent amendments allowing the inclusion of new substances to the list of substances established by the 1928 Opium Act[1] (Table 1) (EMCDDA, 2018). Between 1997 and 2018, 25 NPS were placed under control, including 2C-B and 4-FA (Trimbos-instituut 2020), the two NPS for which data on prevalence of use amongst general population are available. As shown in Table 2, past year prevalence of use amongst adults was established at 0,9% for 4-FA in 2016 (Trimbos-instituut 2017). In 2018, prevalence rate remained at the same level for 4-FA, and was estimated at 0,6% for 2C-B. The use of other NPS (mephedrone, synthetic cannabis, methoxetamine and 6-APB) was estimated at 0,1–0,2% (Trimbos-instituut 2019). Additionally, according to the Dutch Poisons Information centre (DPIC) database, poisonings involving NPS increased from 39 in 2013 to 131 in 2017 (i.e. from 4,1% to 10,6% of the total poison exposures), mostly driven by the consumption of phenethylamines such as 2C-X and 4-FA (Hondebrink et al., 2020). The same trend was observed for consumer samples involving NPS submitted to the Dutch Drugs Information and Monitoring System (DIMS) (Table 3). After the control of 4-FA in 2017 incidents involving this substance submitted to the DIMS considerably decreased (Trimbos-instituut 2019). Yet, its ban led to a diversion to an alternative legal substance such as 4-FMA (a 4-FA-related substance misleadingly sold as its illegal counterpart) in the drug market as the proportion of incidents associated with this substance have progressively risen over time (Trimbos-instituut 2020). Finally, data from forensic samples show that the proportion of NPS-related fatal poisonings represented 2,5% of drug-induced deaths in 2013, going up to 3,1% in 2017 (Table 4). This upward trend was also led by phenethylamines, especially by 4-FA, whose implication showed a two-fold increase over that period (Hondebrink et al., 2020).

4.2. General law—Hybrid control model

In Ireland, along with the prohibition of 'headshops' or any supply-related act (sale, importation, exportation or advertisement) involving harmful psychoactive substances by the 2010 Criminal Justice (Psychoactive Substances) Act[2], NPS were firstly controlled since 2010 through the statutory instrument Misuse of Drugs Act 1977 (Controlled Drugs) (Declaration) Order 2010 (S.I. 199 of 2010)[3] (EMCDDA, 2013; Point, 2012).As a result, more than 200 substances were controlled under the Misuse of Drugs Act 1977[4] (EMCDDA, 2019). Nowadays, NPS are regulated by the Misuse of Drugs (Amendment) Act 2016[5]

[1] Opiumwet, Ministerie van Volksgezondheid en Milieuhygiëne (1928).

[2] Criminal Justice (Psychoactive Substances) Act 2010.

[3] Misuse of Drugs Act 1977 (Controlled Drugs) (Declaration) Order 2010 (S.I. 199 of 2010).

[4] Misuse of Drugs Act, 1977.

[5] Misuse of Drugs (Amendment) Act 2016.

Table 1
NPS control measures implemented by selected countries.

Typology	Country	Legal approach	Year of implementation	Legal Instrument(s)
General law – Individual listing	The Netherlands	Statutes	1997-2018	Amendments to the 1928 Opium Act
General law – Hybrid control model	Ireland	Statutes	2010	Criminal Justice (Psychoactive Substances) Act 2010
			2016	Misuse of Drugs (Amendment) Act 2016
	France	Regulations (Minister of Health)	2012	Legislative order of 27 July 2012 modifying legislative order dated 22 February 1990 that set the list of substances classified as narcotics (cathinone derivatives)
			2015	Legislative order of 19 May 2015 modifying decree dated 22 February 1990 that set the list of substances classified as narcotics (1st & 2nd SCRAs generation)
			2015	Legislative order of 6 November 2015 modifying decree dated February 22, 1990, that set the list of substances classified as narcotics (NBOMe derivatives)
			2017	Legislative order of 31 Mars 2017 modifying decree dated February 22, 1990, that set the list of substances classified as narcotics (3rd SCRAs generation)
NPS-specific law – Individual listing	Czech Republic	Regulations (Government)	2014	Government regulation No 463/2013 Coll., on the lists of addictive substances Government Regulation No.30/2018 Coll., changed the list of addictive substances Government Regulation No.242/2018 Coll., changed the list of addictive substances
	Portugal	Regulations (Minister of Health)	2014	Law 13/2012 of 26 March Decree-Law 15/93 of 22 January Regional Decree 28/2012/M of 25 October Parliament Resolution 5/2013 of 4 January Decree-Law 54/2013 of 17 April Ordinance 154/2013 of 17 April
NPS-specific law – Generic model	Germany	Statutes	2016	2016 German New Psychoactive Substances Act (NpSG)
	Belgium	Regulations (Minister of Public Health, Minister of Justice, Minister of the Interior, Minister of Finances)	2017	Royal Decree of 6 September 2017, regulating narcotic and psychoactive substances
	Poland	Regulations (Minister of Health)	2018	Amendments to the Act of 29 July 2005 on counteracting drug addiction
NPS-specific law – Blanket ban	England & Wales	Statutes	2016	Psychoactive Act 2016
	Scotland			

which contains a combination of generic control and individual listing of substances including phenethylamines, synthetic cannabinoids (SCRAs), synthetic opioids, benzodiazepines, herbal highs, as well as other stimulants and sedatives substances (Health Research Board, 2017). As shown in (Table 2, past year NPS prevalence rate amongst general Irish population (15–64 years old) fell from 3,5% to 0,8% between 2010 and 2011 and 2014–15, while amongst young adults (15–34 years old) it decreased from 6,7% to 1,6% over the same period (Alcohol NACoDa 2015). Besides, the number of acute poisonings associated with 'other and unspecified drugs' (indicator used as a proxy considering that most of the substances classified under this label are very likely to be NPS given difficulties in identification of new substances) has represented a stableproportion (around one-fifth) of all non-fatal overdoses and intentional self-poisoning hospital admissions registered by the Hospital In-Patient Enquiry (HIPE) between 2010 and 2018 (Point, 2012; Board, 2018). Despite the small number of fatal overdoses associated with the consumption of NPS in Ireland, this figure more than doubled between 2010 and 2015 (from 6 to 15), decreasing afterwards to stabilise at 5 by 2017 (HR Board, 2019; HR Board, 2019).

In France,where there is no official definition of NPS, their legal control operates through their incorporation into the list of narcotic drugs as established by the legislative order of 1990.[6] In 2012 France firstly introduced a generic regulation, placing under control synthetic cathinones[7] (Table 1). NPS are currently controlled through a combination of individual listing and generic approach resulting in the control of more than 150 substances, including synthetic cathinones, synthetic cannabinoids and NBOMe analogues[8] (OFDT, 2018; Martinez, 2013; Protais and Blanchon, 2021). As shown in Table 2, experimental use of synthetic cannabinoids (the only NPS for which population-based data is available) has decreased (from 1,7% to 1,3% between 2014 and 2017) after their first classification as narcotic drugs in 2015. Regarding health harms, the Oscour Network led by Public Health France, registered more than 13 thousands drug-related hospital admissions in 2015 (Table 3), of

[6] Arrêté du 22 février 1990 fixant la liste des substances classées comme stupéfiants (NOR : SPSM9000498A).

[7] Arrêté du 27 juillet 2012 modifiant l'arrêté du 22 février 1990 fixant la liste des substances classées comme stupéfiants et la liste des substances psychotropes [molécules dérivées de la cathinone, 4-méthylmethcathinone ou méphédrone, amfépramone] (NOR AFSP1230815A).

[8] Arrêté du 19 mai 2015 modifiant l'arrêté du 22 février 1990 fixant la liste des substances classées comme stupéfiants (NOR: AFSP1511929A). Arrêté du 6 novembre 2015 modifiant l'arrêté du 22 février 1990 fixant la liste des substances classées comme stupéfiants (NOR: AFSP1526800A). Arrêté du 31 mars 2017 modifiant l'arrêté du 22 février 1990 fixant la liste des substances classées comme stupéfiants (NOR: AFSP1710288A).

Table 2
NPS use amongst adults & young adults, available data 2010–2019 (%).

The Netherlands		2016	2018	
Past year prevalence				
2C-B			0,6	
4-FA		0,9	0,9	
Other NPS			0,1 - 0,2	
Ireland		**2010-11**	**2014-15**	
Lifetime prevalence (15-64)			3,5	
Past year prevalence (15-64)		3,5	0,8	
Past month prevalence (15-64)			0,1	
Lifetime prevalence (15-34)			6	
Past year prevalence (15-34)		6,7	1,6	
Past month prevalence (15-34)			0,1	
France	**2014**	**2015**	**2017**	
Lifetime prevalence (18-64)				
Synthetic cannabinoids	1,7	NA	1,3	
Czech Republic	**2011**	**2015**	**2018**	**2019**
Lifetime prevalence (15-64)	1,4	4,5	1,2	3,2
Past year prevalence (15-64)	0,6	1,2	0,2	1,0
Past month prevalence (15-64)	0	0,4	0,1	0,1
Lifetime prevalence (15-34)	1,6	6,8	1,8	3,9
Past year prevalence (15-34)	0,6	1,6	0,5	1,0
Past month prevalence (15-34)	0	0,3	0,2	0,3
Portugal		**2012**	**2016-17**	
Lifetime prevalence (15-74)		0,4	0,3	
Past year prevalence (15-74)		0,1	0,2	
Lifetime prevalence (15-34)		0,9	0,5	
Past year prevalence (15-34)		0,3	0,4	
Germany	**2012**	**2015**	**2018**	
Lifetime prevalence (18-64)	0,6	2,8	2,6	
Past year prevalence (18-64)	0,2	0,9	0,9	
Past month prevalence (18-64)	0,1	0	0,1	
Lifetime prevalence (12-17)		0,1		0,1
Past year prevalence (12-17)		0		0,1
Past month prevalence (12-17)		NR		NR
Belgium		**2013**	**2018**	
Past year prevalence (15-64)		0,1	0,3	
Poland	**2010**	**2012**	**2013**	**2018**
Lifetime prevalence (15-64)		1,4		3,9
Past year prevalence (15-64)		0,2	1	1
Past month prevalence (15-64)		0	1	0,2
Lifetime prevalence (18)	11,4		5,2	2,6
Past year prevalence (18)	7,2		2	1,5
Past month prevalence (18)	1		1	0,7
England & Wales	**2014-15**	**2016-17**	**2017-18**	**2018-19**
Lifetime prevalence (16-59)	2,8	2,4	2,5	2,5
Past year prevalence (16-59)	0,9	0,4	0,4	0,5
Lifetime prevalence (16-24)	6,1	4,2	4,7	4,3
Past year prevalence (16-24)	2,8	1,2	1,2	1,4
Scotland	**2014-15**	**2016-17**	**2017-18**	**2018-19**
Lifetime prevalence (16-59)	1,6		1,8	
Past year prevalence (16-59)	0,4			

which 36% were associated with multiple or unknown substances (they represented 52% in 2010) (Brisacier, 2019). Besides, 288 NPS-related intoxications have been registered by the National Agency for Medicines Security (ANSM) between 2009 and 2014 (OFDT 2019). According to ANSM, acute intoxications associated with NPS mainly involve synthetic cathinones (142 cases between 2009 and 2014), synthetic cannabinoids (11 cases between 2011 and April 2017), psychedelics and synthetic opioids (8 intoxications between 2012 and 2017, of which 2 having fatal consequences, associated with nonmedical use of fentanyl analogues) (ANSM, 2017; Martinez et al., 2018). Regarding NPS-related mortality, one of the national toxicological registers (DRAMES) show a small but increasing number of annual drug-induced deaths associated with NPS between 2013 and 2018 (from 2 to 18 cases), stabilising in 2019 (8 cases) (Table 4). According to this source, substances involved in NPS-induced deaths (alone or in combination) are mainly synthetic cathinones, GHB, phenethylamines and synthetic opioids (CEIP, 2020, 2019, 2018, 2017, 2016). It is worth noting that variations in the number of deaths registered by DRAMES must be interpreted with caution as the latter is a voluntary national system in which the participation of toxicologists is voluntary and thus varies from year to year (Brisacier et al., 2019).

4.3. NPS-specific law—Individual listing

In the Czech Republic, the control over new substances was established by means of individual listing of substances annexed to the Act No. 167/1998 Coll. on addictive substances[9] until 2013. Since the enactment of the Government Regulation No. 463/2013 Coll.[10] in 2014, the list of new controlled substances is regularly updated via amendments to this new NPS-specific legal instrument. In 2017, 63 new substances were placed under the provisions of this specific regulation (EMCDDA 2018a). In 2018, the list of controlled substances was extended to 82 new substances when two additional government regulations (Government Regulation No. 30/2018 Coll.[11] and Government Regulation No. 242/2018 Coll.[12]) came into force (Mravčík et al., 2020; EMCDDA 2018a). As shown in Table 2, prevalence rates markedly increased between 2011 and 2015 in Czechia: lifetime prevalence rates rose from 1,4% amongst general population (15–64 years old) and 1,6% amongst young people (15–34 years old) in 2011, to 4,5% and 6,8% respectively in 2015. Afterwards, rates significantly fell to 1,2% and 1,8% in 2018 respectively. The same trend was observed for past-year and past-month prevalence rates (Mravčík et al., 2020). Additionally, data from the National Register of Hospitalisations evidenced 70 admissions to acute care hospital wards for drug intoxication involving 'other and unspecified drugs' (proxy indicator) in 2010 (Table 3). Afterwards, thisfigure reached a peak of 94 cases in both 2013 and 2017, though it has represented around 30% of drug-related poisonings over time (Mravcík et al., 2021). Finally, data from the Czech general mortality register show that fatalities involving 'unspecified drugs'increased from 8 cases in 2010 to 14 cases in 2016 (Table 4). In 2019, only 5 cases of death associated with NPS were officially reported in Czechia (Mravcîk et al., 2021; Chomynová and Grohmannová, 2015; National Monitoring Centre for Drugs and Addiction, 2016).

In Portugal, the first legal measure against NPS was adopted in 2012, when mephedrone was added to the list of controlled substances through the enactment of Law 13/2012[13] that modified Decree-Law 15/93[14] on the legal regime applicable to the trafficking and consumption of narcotics and psychotropic substances (SICAD 0000; EMCDDA 2011). Additionally, Regional Decree 28/2012M[15] updated the legal framework for psychoactive substances and prohibited the sale of 'legal highs' (NPS) in Madeira Island (SICAD 2015). In 2013,following a recommendation from the Parliament via Resolution 5/2013[16], Decree-Law 54/2013[17] was issued by the Government, to provide a specific legal framework for the prevention and protection against advertisement and trade on any new psychoactive substance intended for human consumption that may be dangerous or pose a risk for human beings or public health. This included the prohibition of the production, export, advertisement, distribution, sale, or simple supply of NPS, as well as a coordinated action led by the General Directorate for Intervention on Addictive Behaviours and

[9] Act No. 167/1998 Coll., on Addictive Substances and on the Amendment of Certain Other Acts.
[10] Government Regulation No. 463/2013 Coll., on the lists of addictive substances.
[11] Government Regulation No. 30/2018 Coll., changed the list of addictive substances.
[12] Government Regulation No. 242/2018 Coll., changed the list of addictive substances.
[13] Lei n.º 13/2012 de 26 de março.
[14] Decreto-Lei n.º 15/93 de 22 de janeiro.
[15] Decreto Legislativo Regional n.º 28/2012/M de 25 de outubro.
[16] Resolução da Assembleia da República n.o 5/2013.
[17] Decreto-Lei n.º 54/2013 de 17 de abril.

Table 3
NPS-related poisoning/intoxication cases.

The Netherlands	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Number of samples or inquiries involving new psychoactive substances (NPS)										
Consumer samples (DIMS)				754	1161	1357	1694	1350		
as a % of total consumer samples				*7,4%*	*10,9%*	*11,4%*	*15,1%*	*11,3%*		
Source: Drugs Information and Monitoring System (DIMS) | Drugs Informatie en Monitoring Systeem (DIMS)										
Poison centre exposures				39	88	97	126	131		
as a % of total poison exposures				*4,1%*	*8,5%*	*9%*	*11,3%*	*10,6%*		
Source: Dutch Poisons Information Centre (DPIC) | Nationaal Vergiftigingen Informatie Centrum (NVIC)										
Ireland	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of admissions to hospital for non-fatal overdose involving drugs										
Other and unspecified drugs	945	924	908	878	937	790	886			
as a % of total non-fatal overdose cases	*21%*	*22%*	*21%*	*21%*	*22%*	*20%*	*21%*			
Number of hospital admissions for intentional self-poisoning involving drugs										
Other and unspecified drugs	588	235	546	507	518	427	476			
as a % of total intentional self-poisoning cases	*20%*	*8%*	*19%*	*19%*	*19%*	*17%*	*18%*			
Source: HIPE, Healthcare Pricing Office										
France	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Emergency care hospitals admissions as a % of total admissions for intoxication										
Multiple or unknown substances	52%					36%				
Source: Oscour Network, Public Health France | Réseau Oscour, Santé Publique France										
Czech Republic	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of hospitalizations for drug intoxication in emergency care hospitals										
Other and unspecified drugs (T40.4, T40.6, T40.9)	70	68	80	94	81	76	79	94	65	79
as a % of total hospitalizations for illicit drug intoxication	*30,2%*	*32,5%*	*32,5%*	*31,1%*	*26,0%*	*28,1%*	*27,0%*	*33,6%*	*26,2%*	*31,0%*
Source: Institute of Health Information and Statistics of the Czech Republic | Ústav zdravotnických informací a statistiky ČR										
Portugal	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of intoxications involving addictive substances										
Other and unknown drugs						98	72			
as a % of total intoxications involving addictive substances						*8%*	*6%*			
Source: Poison Information Centre | Centro de Informação Antivenenos (CIAV)										
Germany	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of NPS-related cases										
NPS-related mono & polydrug poisonings								49	63	
Source: Phar-Mon NPS project & Poison information Centre (GIZ)										
Belgium	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of telephone inquiries received at the Poison Centre										
NPS and unknown substances	73	43		52						
as a % of total telephone enquiries related to illicit drugs	*21,7%*	*12,4%*		*25,5%*						
Source: Belgian National Poison Centre | Centre Belge Antipoison										
Poland	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Likely medical interventions induced by new psychoactive substances										
NPS-induced poisonings	562	118	299	1 078	2 513	7 283	4 369	4 324	4 260	2 362
Source: Poisonings Control Centre, General Sanitary Inspectorate										
England & Wales	**2010-11**	**2011-12**	**2012-13**	**2013-14**	**2014-15**	**2015-16**	**2016-17**	**2017-18**	**2018-19**	**2019-20**
Number of patients admitted to hospital by primary diagnosis: poisoning										
Other and unspecified narcotics (T40.6)					749	870	880	864	956	952
Source: The Health and Social Care Information Centre, Hospital Episode Statistics for England										
Scotland	**2010-11**	**2011-12**	**2012-13**	**2013-14**	**2014-15**	**2015-16**	**2016-17**	**2017-18**	**2018-19**	**2019-20**
Drug-related general acute stay rates (per 100,000 population)										
Sedative/hypnotic (incl. includes new or unlicensed benzodiazepines)	8							28		
as percentage of general acute stays	*7%*							*14%*		
Other stimulants	5				12			8		
as percentage of general acute stays	*4%*				*8%*			*4%*		
Source: NHS Services Scotland - National Statistics										

Table 4
NPS-related deaths.

The Netherlands	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Number of forensic samples										
Forensic samples involving new psychoactive substances (NPS)				362	574	288	338	330		
as a % of total forensic samples				*2,5%*	*3,9%*	*2,1%*	*2,7%*	*3,1%*		
Source: Netherlands Forensic Institute (NFI) | Nederlands Forensische Instituut (NFI)										
Ireland	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of poisoning deaths	339	377	356	401	370	370	368	376		
NPS	6	5	7	17	15	15	7	5		
as a % of total poisoning deaths	*1,8%*	*1,3%*	*2,0%*	*4,2%*	*4,1%*	*4,1%*	*1,9%*	*1,3%*		
Source: National Drug-Related Deaths Index (NDRDI) - Health Research Board										
France	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of fatal overdoses	276	316	346	328	283	395	449	472	506	551
Fatal overdoses involving NPS (alone or in combination)	1	1	1	2	5	15	19	14	18	8
as a % of total fatal overdoses	*0,4%*	*0,3%*	*0,3%*	*0,6%*	*1,8%*	*3,8%*	*4,2%*	*3,0%*	*3,6%*	*1,5%*
Source: Deaths Related to Medecines and Substance Abuse | Décès en Relation avec l'Abus de Médicaments Et de Substances (DRAMES)										
Czech Republic	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of fatal drug overdoses in the general mortality register	29	22	32	39	48	57	48		59	51
Other and unspecified drugs	8	5	8	9	11	10	14		10	5
as a % of total fatal drug overdoses involving illicit drugs	*27,6%*	*22,7%*	*25,0%*	*23,1%*	*22,9%*	*17,5%*	*29,2%*		*16,9%*	*9,8%*
Source: Institute of Health Information and Statistics of the Czech Republic | Ústav zdravotnických informací a statistiky ČR										
Portugal	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of deaths by overdose	52	19	29	22	33	40	27	38	49	63
Synthetic drugs		1	1	3	2	1	3	3	1	2
as a % of total deaths by overdose		*5,3%*	*3,4%*	*13,6%*	*6,1%*	*2,5%*	*11,1%*	*7,9%*	*2,0%*	*3,2%*
Source: National Institute of Legal Medicine and Forensic Sciences | Instituto Nacional de Medicina Legal e Ciências Forenses										
Germany	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of drug-related deaths			944	1002	1032	1226	1333	1272	1276	1398
NPS monodrug use			1	3	16	19	35	9	7	9
NPS polydrug use			11	2	13	20	41	19	12	10
NPS total			12	5	29	39	76	28	19	19
as a % of total drug-related deaths			*1,3%*	*0,5%*	*2,8%*	*3,2%*	*5,7%*	*2,2%*	*1,5%*	*1,4%*
Source: Federal Criminal Police Office | Bundeskriminalamt (BKA)										
Belgium	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Drug-related deaths			13	40			60	62		
NPS-related deaths			3	2			5	5		
as a % of total drug-related deaths			*23,1%*	*5%*			*8,3%*	*8,1%*		
Source: Belgium Early Warning System on Drugs										
Poland	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Number of drug-induced deaths										
NPS-induced deaths				3	3		7			
as a % of total drug-induced deaths				*1,2%*	*1,1%*		*3,4%*			
Source: Poisonings Control Centre, General Sanitary Inspectorate										
England & Wales	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Deaths mentioning specific substances on the death certificate										
New psychoactive substances	23	31	56	63	82	114	123	62	126	125
as a % of total drug-related deaths	*0,8%*	*1,2%*	*2,2%*	*2,1%*	*2,5%*	*3,1%*	*3,3%*	*1,7%*	*2,9%*	*2,8%*
Source: Office for National Statistics										
Scotland	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
Drug-related deaths, on the basis of the ONS 'wide' definition										
Deaths involving NPS	11	47	47	113	114	112	345	363	588	802
as a % of total drug-related deaths	*1,6%*	*6,3%*	*6,4%*	*16,5%*	*15,3%*	*13,8%*	*34,6%*	*34,7%*	*44,8%*	*57,0%*
Source: National Records of Scotland										

Dependencies (SICAD). This legislation was accompanied by Ordinance 154/2013,[18] which updated the list of new psychoactive substances under control (SICAD 2015). Those regulations introduced individual listing of substances classified into six schedules. Since their enactment lifetime prevalence rates of NPS use have decreased, especially amongst young people aged 15–34 years-old (from 0,9% to 0,5% between 2012 and 2016–17), while past-year consumption slightly increased over the same period (Table 2) (SICAD, 2020). Moreover, there were no NPS-related admissions to Portuguese hospitals until 2014 (EMCDDA, 2014). Afterwards, registers from the national Poisoning Information Centre showed that about 10% of total information inquiries received between 2015 and 16 were associated with unknown drugs (Table 3). Finally, special mortality registers showed a downward trend in fatal overdoses associated with NPS use, as they represented 14% of total fatal overdoses registered in 2013, falling to 3% in 2019 (Table 4) (SICAD, 2020).

4.4. NPS-specific law—Generic model

In Germany, a series of amendments to the 1981 German Federal Narcotics Act (Betäubungsmittelgesetz - BtMG[19]) were firstly introduced as a response to NPS. Thus, about 90 new psychoactive substances were placed under control between 2007 and 2015 (Pfeiffer-Gerschel et al., 2012; 2015; EMCDDA 2013). In November 2016, the New Psychoactive Substances Act (NpSG)[20] was enacted to protect population's health against the risks associated with the consumption of NPS. This specific regulation introduced a generic approach that replaced the individual listing by banning entire categories of substances or NPS drug families. It aimed to reduce the use of NPS by restricting their availability through the introduction of an administrative ban on purchase and possession of NPS, and criminal penalties for supplying them (Sipp at al., 2018).

As shown in Table 2, the experimental and regular use of NPS amongst German adults (18–64 years old) increased between 2012 and 2015 (from 0,6% to 2,8%, and from 0,2% to 0,9% respectively). Yet a slight decrease in experimental NPS use was observed lately (2,6% in 2018), while regular use remained stable at 0,9% of the adult population (EMCDDA, 2013; Karachaliou et al., 2019; Piontek et al., 2018). In 2015, Germany started collecting data on NPS-related intoxications through the Phar-Mon NPS project which, in cooperation with a poison information centre (Giftinformationszentrale - GIZ), registered 49 cases of poisoning due to NPS in 2017 and 63 in 2018 (Karachaliou et al., 2019; Piontek et al., 2018). As shown in Table 4, 12 fatalities associated with the consumption of NPS (alone or in combination with other substances) were registered in 2012, increasing in the following years (Dammer et al., 2016; EMCDDA, 2013; Pfeiffer-Gerschel et al., 2015). The number of NPS-induced deaths went up to 76 in 2016, decreasing to 28 in 2017 and 19 in 2019 (Dammer et al., 2018; Neumeier et al., 2019; Neumeier et al., 2020).

In Belgium, NPS were individually placed under control by amendments to the schedules of the 1921 Drug Law[21] until 2014, when the law was adapted to allow generic control of new substances (EMCDDA 2017). In September 2017, the adoption of a Royal Decree on narcotics and psychoactive substances[22] introduced an NPS-specific generic regulation that placed under control groups of substance including synthetic cathinones, amphetamine derivatives, tryptamines, synthetic cannabinoids, piperazines and fentanyl derivatives (Van Havere et al., 2020). According to the Belgian National Health Survey, past year prevalence rate of NPS use amongst general population (15–64 years old) was estimated at 0,1% in 2013, slightly increasing to 0,3% in 2018 (Gisle, 2014; Gisle and Drieskens, 2018). Available data on NPS-related harms is scarce in Belgium, yet telephone inquiries received by the Belgian national Poison Centre show that 227 NPS-related intoxications (including mephedrone, GHB/GBL and other unknown/unidentified substances) were registered between 2010 and 2013, which represents 19% of the total number of inquiries received over time (Plettinckx et al., 2012, 2014). Additionally, post-mortem toxicology results reported by the Belgian Early Warning System on Drugs (BEWSD) highlight that 15 fatal poisoning were associated with the consumption of NPS – namely 4-MA, PMMA, GHB – between 2012 and 17 (EMCDDA 2016, 2018). Later, Novel synthetic opioids (NSO) have been implicated in a higher number of deaths: in 2016 and 2017, U-47,700 (a fentanyl analogue) was involved in 5 cases (EMCDDA 2019; EMCDDA 2018c).

In Poland, continual amendments to the 2005 Act on Counteracting Drug Addiction[23] were firstly introduced in 2008,placing under control more than 50 synthetic and natural NPS (Malczewski and Misiurek, 2014). In 2019, two new substances (BZP, JWH-18) and 15 plants were placed under control (Jablonski and Malczewski, 2014). Additional amendments to this legal instrument as well as to the Act on State Sanitary Inspection[24] were issued in 2010 (Dabrowska et al., 2017; Jablonski and Malczewski, 2014; Malczewski et al., 2015). Along with the nationwide closure of head shops, those regulations introduced a definition of NPS as a natural or synthetic substance used instead or for the same purpose as a narcotic drug or psychotropic substance, whose manufacture and commercialisation are not regulated under polish law (EMCDDA, 2014). As a result, mephedrone and several synthetic cannabinoids were placed under control (Jablonski and Malczewski, 2014; EMCDDA 2015). In 2018, individual listing was replaced by the adoption of an NPS-specific instrument, the Regulation of the Minister of Health of 17 August 2018[25] (as amended in 2019) on the list of psychotropic substances, narcotic drugs and new psychoactive substances, which introduced a generic control over five groups of substances: phenethylamines (derivatives of 2-phenethylamines - group I-NPS); synthetic cathinones (derivatives of 2-amino-1-phenylpropan-1-one - group II-NPS); synthetic cannabinoids (group III-NPS); synthetic opioids (derivatives of fentanyl - group IV-NPS); benzodiazepines (group V-NPS) (Malczewski et al., 2020).According to population-based data, lifetime and past-year NPS use increased among adults (15-64 years old) from 1,4% to 0,2% respectively in 2012 to 3,9% and 1% in 2018 (Table 2) (Malczewski et al., 2020, 2013). Experimental and regular uses of NPS amongst Polish final grade secondary school students (only population-based data available) reached their highest level in 2010 (11,4% and 7,2% respectively), going down to 5,2% and 2% in 2013. The downward trend was confirmed in 2018, when lifetime and past-year prevalence of use were estimated at 2,6% and 1,5% respectively (Malczewski, 2019; Jablonski and Malczewski, 2014). Regarding health harms, data from the Poisonings Control Centre show that NPS-induced poisonings declined between 2010 and 2012 (from 562 to 299) following the closure of head shops in November 2010, steady increasing by 2015 when the highest figure was registered (()7 283). In 2019, acute intoxications associated with NPS consumption showed a three-fold decline (only 2 362 poisoning episodes were registered) (Malczewski et al., 2020). Additionally, 3 fatalities associated with the consumption of NPS were registered by the National Consultant in Clinical Toxicology in 2013, and another 3 were identified in 2014 (Malczewski and Misiurek, 2014). In 2016, registers from the Department of Forensic Science of the University of Warsaw covering its metropolitan area showed that 7 deaths were induced by NPS, which represent 15% of the total number of drug-induced deaths in Warsaw area that year. Four NPS-induced deaths were associ-

[18] Portaria n.º 154/2013 de 17 de abril.

[19] Gesetz über den Verkehr mit Betäubungsmitteln (Betäubungsmittelgesetz - BtMG).

[20] Neue-psychoaktive-Stoffe-Gesetz - NpSG.

[21] 24 FEVRIER 1921. Loi concernant le trafic des substances vénéneuses, soporifiques, stupéfiantes, désinfectantes ou antiseptiques.

[22] 6 SEPTEMBRE 2017 - [Arrêté royal réglementant les substances stupéfiantes et psychotropes].

[23] Act of Law of 29 July 2005 on Counteracting Drug Addiction.

[24] Act of 8 October 2010 amending the Act on counteracting drug addiction and the Act on State Sanitary Inspection.

[25] Regulation of the Minister of Health of 17 August 2018.

ated with synthetic opioids (U-47700), 3 to synthetic cathinones and 1 to synthetic cannabinoids (Malczewski, 2019).

4.5. NPS-specific law—Blanket ban

In Great Britain, the first legal response to NPS was the adoption of the Police Reform and Social Responsibility Act in 2011[26], which facilitated the legislative response to NPS introducing a temporary class drug order (EMCDDA, 2018). In 2016, the enactment of the Psychoactive Substances Act 2016 (PSA)[27] replaced the substance-by-substance approach to NPS, criminalising production, supply, or possession with intention to supply of any substance with psychoactive effects. The PSA aimed at reducing NPS use and its related health and social harms amongst general population through cuts in the availability of substances sold both in stores and online (Office H 2018). Under its provisions possession of NPS does not constitute an offence unless it takes place within a custodial institution which, along with the proximity to educational facilities and the use of minors as couriers, is also considered as an aggravating factor for supply offences (EMCDDA, 2018).

In England and Wales, lifetime and past year use of NPS amongst adults decreased between 2014 and 15 and 2016–17 (from 2,8% to 2,4%, and from 0,9% to 0,4% respectively). The same trend was observed amongst young people (16-24 years old), whose lifetime and past year prevalence rates also fell between 2014-15 and 2016-17 (from 6,1% to 4,2%, and from 2,8% to 1,2% respectively). By 2018-19 a slight increase was observed in past year NPS use among adults and youth (Table 2) (Home Office, 2019). Having no data on NPS-specific intoxication episodes, hospital admissions related to poisoning by 'other and unspecified narcotics' were used as a proxy of poisoning by consumption of NPS. In England, hospital admissions classified under this category increased by 27% between 2014 and 15 and 2019–20 (Table 3) (NHS, 2020). According to a study conducted in London, an increase in acute intoxications involving SCRAs and a reduction in those involving cathinones were observed 12 months after PSA came into force (Home Office, 2018). Additionally, according to the Office for National Statistics,[28] drug-related deaths involving NPS have continuously risen since 2010, when 23 fatal poisonings were associated with NPS (Office for National Statistics, 2020). As shown in Table 4, this figure reached 123 registered cases in 2016, temporally halved in 2017 (with only 62 NPS-related deaths) going back to its previous level in 2019 (125 cases). According to the same source, NPS-related fatal poisonings commonly involve synthetic cannabinoids, GHB, benzodiazepine analogues and cathinones (mephedrone): these substances represented 45%, 22%, 21% and 11% of NPS-related deaths in 2019, respectively. It is worth noting that while the presence of cathinones in fatal poisonings has declined over time, according to the previously mentioned source the involvement of benzo-NPS and SCRAs has recently shown an upward trend (Office for National Statistics, 2020).

In Scotland, available data show that lifetime use of NPS amongst adults has slightly increased between 2014 and 15 (1,6%) and 2017–18 (1,8%) (Table 2) (National Statistics, 2019, 2016). As shown in Table 3, the introduction of 2016 PSA may have positively impacted the evolution of acute hospital admission associated with stimulants-NPS (classified as 'other stimulants' by Scottish official statistics), yet the rate of hospital stays associated with sedative/hypnotics, which includes new or unlicensed benzodiazepines (benzo-NPS or 'street' benzodiazepines) that are also controlled by the 2016 PSA, has doubled between 2010 and 11 and 2017–18 (from 7% to 14% of general hospital acute stays) (Scotland NS 2019). Similarly, mortality associated with NPS use has been increasing since 2010, when 11 cases of deaths involving NPS were registered. The number of cases had steadily increased by 2016, when 345 deaths were associated with the consumption of NPS and has continued to grow over time (802 NPS-related deaths were registered in 2019). It is worth noting that this trend is led by the consumption of benzo-NPS, which represent almost 100% of NPS-related deaths in Scotland lately (Scotland NRo 2020).

5. Discussion

Since 2010, NPS-related legal measures started to be adopted across Europe as targeted responses to address the highly dynamic and resilient NPS market. All legislative approaches to controlling NPS are made in accordance with the three United Nations conventions of 1961, 1971 and 1988 (EMCDDA, 2009, UNODC, 2013b). They may either be included within national broad drug control systems (primary or secondary legislation) or emerge as a new independent legal instrument (specific legislation). Three regulatory models may be identified amongst those adopted by countries under study. *Individual listing* establishes lists of substances (schedules) individually classified and placed under national control based ontheir psychoactive effects alongside the assessment of their therapeutic value and potential harm (risk of abuse and dependence) (EMCDDA, 2016). Under this model, legal control may be temporal or permanent, being enacted either through regular legislative processes or through rapid legal procedures that accelerate the standard legislative process (by omitting one or more standard legislative steps or reducing procedural time periods) required to place new substances under permanent control (EMCDDA, 2015). In terms of prevention of NPS use, a decrease (or at least a stagnation) in experimental or regular use has been observed in the three countries that adopted this regulatory model (The Netherlands, Czech Republic, Portugal). Implemented as part of general drug law or as a specific legislation, individual listing provides legal certainty about the control status of potentially harmful substances, yet it may also increase the exposure to potential health risk due to the lengthy procedure that places new substances under national control. Although individual regulation of most used NPS seems to be relatively effective in reducing consumption, it has also led to their replacement by similar more toxic substances. As seen in The Netherlands , slight structural variations to individually controlled substances remain uncovered by legislation, which allows the diversion to new potentially dangerous substances. As a result, this regulatory model may have unintended negative effects on NPS users' health, as an increase in NPS-related acute poisonings and/or fatal overdoses has been observed.

The *generic model* enables control of groups of substances based on their core chemical structure, which is generally similar to already controlled substances (i.e., synthetic cathinones or synthetic cannabinoids). This regulatory model, that may also be implemented within general drug control legislation or as NPS-specific regulations, facilitates legal responsiveness to the emergence of new substances closely related to those already controlled (UNODC 2013a). Although it also requires surveillance and frequent updating due to potential substances' chemical diversification, it may be suitable for countries with a highly dynamic NPS market. As observed in countries that have adopted it, this model does not seem to be particularly efficient in reducing NPS consumption. Only Poland has shown a decrease in experimental and regular NPS use amongst school students (along with an increase in lifetime and past year use amongst general population), while in Germany prevalence rates of NPS use remain stable since the adoption of generic control in 2016, and in Belgium a slight increase in past-year NPS use was observed a year after its introduction in 2017. In terms of potential harmful effects on users' health, an increase in NPS-related poisonings has been observed following the introduction of generic controls in Germany and Poland. Furthermore, NPS-related deaths have increased in two (Belgium and Poland) out of three countries having adopted this regulatory model.

A *combination of individual listing and generic control* was implemented by France and Ireland, allowing the control of specific dangerous sub-

[26] Police Reform and Social Responsibility Act 2011.
[27] Psychoactive Substances Act 2016.
[28] Office for National Statistics, Deaths related to drug poisoning by selected substances.

stances as well as potentially harmful families of NPS (SCRAs, synthetic cathinones and NBOMe derivatives). In terms of legal prevention and control, this hybrid model has been successful in reducing regular NPS use. In France, the ban on SCRAs seems to have a positive impact on deterring their use, though it is impossible to know whether the ban on synthetic cathinones, NBOMe derivatives and other individual substances have impacted their use as available data only cover experimental use of SCRAs. Regarding effects on users' health,no homogenous trends have been observed. Available data evidence a stable (Ireland) or downward (France) trend in NPS-related intoxications along with an increased in NPS-related deaths in France and a decrease in Ireland. Of special interest is the increase in fatal overdoses involving synthetic cathinones (banned in 2012) observed in France. This hybrid model has been successful in reducing NPS use yet their involvement (especially synthetic cathinones and, to a lesser extent, SCRAs) in acute intoxications and fatal overdoses has increased over time, which may suggest higher levels of potency/toxicity innew substances that have replaced those banned (OFDT 2019).

Finally, a *blanket ban* is a specific legal measure that applies to or affects all or most new psychoactive substances available in the drug market. As adopted in Great Britain (England & Wales, and Scotland), blanket bans are aimed at the disruption of the entire supply chain of untested, unknown, and potentially harmful new psychoactive substances intended for human consumption, regardless of their chemical structure and potential variations. Although this regulatory model seeks to dramatically reduce NPS use by encompassing the largest possible variety of new substances, its effectiveness in preventing use seems to be very limited. Only in England & Wales a temporarily decline in NPS use was observed immediately after the enactment of the blanket ban (stagnating afterwards), while in Scotland it has never stopped rising. Moreover, NPS-related intoxications and deaths have continuously been on the rise, reaching their highest registered levels after theintroduction of this legal change. Although the scope of substances controlled under the blanket ban has changed over time, notably with third generation synthetic cannabinoids placed under the Misuse of Drugs Act 1971 (MDA) since December 2016, the blanket ban adopted was only partially and temporary effective in preventing NPS use, while it has shown an overall negative indirect effect on NPS users' health as evidenced by the increase in NPS-related intoxications and deaths.

Regardless of the regulatory model adopted, NPS-related control measures have led to either the production of new structurally close substances (individual classification) or to introduction new drugs families (generic classification) into the drug market. Even in countries where a blanket ban was introduced, the emergence of new substances has not ceased. Instead, the development of new substances along with changes in the supply chain have been observed (Office H 2018). Moreover, in countries where head shops were available (Ireland, Poland and Great Britain), their closure due to an administrative measure or as an indirect consequence of a blanket ban implied a shift to either online suppliers or street dealers which reduced immediate availability (sometimes also increased prices) and ultimately prevented NPS use. In Poland, the implementation of large prevention campaigns may also explain the reduction in NPS consumption (Malczewski and Struzik, 2012).

As shown by our study findings, control measures – particularly individual listing - may be relatively effective in preventing NPS use, at least in the short-term. However, as observed in The Netherlands, France, Poland and Great Britain, control measures are very likely to affect the purity and potency of substances, which in turn may have an indirect negative impact on users' health (adverse reactions, poisonings, and fatal overdoses). In fact, NPS-related acute poisonings and fatal overdoses have not been reduced after the enactment of control measures. To the contrary, an increase in NPS-related poisonings and deaths has been observed in most of the countries having introduced control measures, regardless the regulatory model adopted. It seriously questions the capacity of punitive measures to avoid substances deleterious effects on users' health. Furthermore, the control of an increasing number of substances has also been criticized for its negative impact on limiting research on new substances whose potential therapeutic benefit and actual harm potential remain unexplored due to licensing requirements (Peacock et al., 2019; Kavanagh and Power, 2014). This is particularly relevant from a public health perspective, as the absence of scientific evidence on substances pharmacological and toxicological profiles restricts the capacity for appropriate clinical management of NPS-related poisoning and overdose episodes (Peacock et al., 2019; Zamengo et al., 2019). Moreover, there is a need for reference samples, technical laboratory equipment enabling the accurate identification of new substances, recognised scientific methods to determine substances' nature and chemical substitution patterns, as well as specialised technologies and information/intelligence exchange systems to communicate reliable information about NPS-related risks to healthcare professionals and users (Peacock et al., 2019).

Furthermore, the enforcement of new legislation may be in practice difficult and time consuming namely due to the transnational nature of the NPS markets, with chemical substances (precursors and cutting agents) continuously arriving from China and India into consumer countries (Peacock et al., 2019; van Amsterdam et al., 2013; Duffert, 2014). In that regard, of special interest is the role played by the internet (surface and deep-web) in driving the rapid evolution of NPS markets through the provision of information on chemical products and equipment that facilitates their development at a global level, while hindering regulation and monitoring by national and supranational agencies (Seddon, 2014; Peacock et al., 2019).

Finally, as NPS usually mimic psychoactive effects of traditional drugs, their use seems to be less prevalent in countries with a less punitive approach to drug use (Portugal, Czech Republic, The Netherlands). Yet, according to available evidence, classic illicit drugs such as cannabis may be adulteratedwith synthetic cannabinoids to make their trade more profitable (Somerville et al., 2019; Kosmicare 2022; Lamy et al., 2017). As a result, healthcare, toxicologist and forensic services, as well as law enforcement agencies are ill-prepared to respond to a challenging ever evolving drug situation (Kavanagh and Power, 2014).

Hence, interventional public health laws such as NPS-related legislations have overall failed in their attempt to have a direct positive influence on users' health outcomes. The long-term impact of these legal measures seems to be limited, with illicit individual substances or generic drug classes continuously being replaced by new uncontrolled ones. Thus, regardless of the regulatory model implemented, the effectiveness in reducing NPS prevalence of use (legal prevention and control) is also limited in scope and time. Moreover, control measures have unintendedly produced harmful effects on users' health (legal aetiology) such as an overall oincrease in acute intoxications and deaths due to the higher levels of toxicity and potency observed in both recently banned and new uncontrolled substances available on the drug market.

In the light of the overall failure of the prohibitionist approach to NPS, the regulation of drug markets may appear as a more successful policy strategy to limit deleterious effects of drug policy as well as negative consequences of recreational drug use. As scholars in the field have already pointed out (Seddon, 2014; Ritter, 2010), the regulatory challenges posed by NPS represent an opportunity to rethink the traditional approach to drugs that primarily relay on national and supra-national agencies that use law enforcement to dissuade and punish offenders. Instead, regulatory innovation may incorporate private actors such as drug users themselves and healthcare professionals to design and implement more effective approaches to drug-related health and social problems. Drug policy should be built on available evidence pointing towards the inadequacy of punitive legal measures aimed at eradicating drug use. By ignoring the psychological and social underlying factors driving the use of psychoactive substances – notably search for self-exploration, pleasure, emotional and physical enhancement, and socialisation – drug policy fails in providing a coherent approach to public health implications of drug use (Reuter and Pardo, 2017; Larney et al., 2021).

This study provides some new evidence on the effectiveness of different legal and policy approaches to NPS use, particularly on the harmful effects of control measures on drug users' health. Yet, it is worthmentioning some study limitations, which are notably related to the lack of specific and heterogeneous data on NPS health indicators (e.g., prevalence of use, acute intoxications, and deaths) and timeseries allowing for an analysis of trends over time. As above-mentioned, scarcity of accurate data on substances chemical composition may be explained by the absence of adequate equipment to identify new substances within hospitals, but also at toxicologists, forensic and law enforcement services. Scholars in the field have already suggested that reports of acute (intoxication/poisoning) or chronic health problems (addictions, psychiatric consequences) associated with unknown substances identified through surveillance data can be used as indirect indicators of NPS use (Martinez et al., 2018). Finally, there is a lack of time perspective allowing the establishment of confirmed trends to inform the elaboration of NPS-specific legal responses.

6. Conclusions

The range of drugs consumed today across Europe is noticeably diverse while patterns of drugs use remain marked by polydrug use (EMCDDA 2021). As for other controlled drugs, legal status does not seem to be a driven for NPS consumption. Instead, a displacement to either traditional drugs or newly appeared (potentially dangerous) substances due to falls in NPS availability has been observed, especially amongst vulnerable populations (Office H 2018; Vidal Giné et al., 2014; van Riel et al., 2022). Thus, policy measures implemented across Europe to counter the emergence of NPS have not been markedly effective in either deterring their use or preventing harms on users' health. Instead, they have been accompanied by increased levels of toxicity and health harms for users. Therefore, there is a need for innovative regulatory initiatives that go beyond supranational bodies and state-centred law enforcement responses focused on dissuading drug use, to design and implement policy strategies that effectively reduce drug-related health harms.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Jessica Neicun: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Visualization. **Andres Roman-Urrestarazu:** Writing – review & editing, Supervision. **Katarzyna Czabanowska:** Writing – review & editing, Supervision.

Appendix 1

Table A1

Table A1
Definitions of NPS and health related indicators.

Country	NPS legal definition	NPS-related poisoning/intoxication cases	NPS-related deaths
The Netherlands	New Psychoactive Substances (NPS) are substances that have a similar effect to 'traditional' illegal drugs, but are not (yet) covered by drug-related legislation. Source: Trimbos-instituut, 2019	Consumer samples and poisoning inquiries involving new psychoactive substances (NPS)	Forensic samples containing new psychoactive substances (NPS)
Ireland	"Psychoactive substance" means a substance, product, preparation, plant, fungus or natural organism which has, when consumed by a person, the capacity to (a) produce stimulation or depression of the central nervous system of the person, resulting in hallucinations or a significant disturbance in, or significant change to, motor function, thinking, behaviour, perception, awareness or mood, or (b) cause a state of dependence, including physical or psychological addiction. Source: Psychoactive Substances Act 2010	Hospital admission for non-fatal overdose involving other and unspecified drugs Hospital admissions for intentional self-poisoning involving other and unspecified drugs	Poisoning deaths involving New Psychoactive substances (NPS)(including Etizolam) - Individual deaths
France	No official definition. NPS are understood as a vast group of products that are collectively referred to as "new drugs". These are psychoactive products whose effects are similar to those of known products, such as amphetamines, cocaine and ketamine, but whose molecular structure is different. This difference means that narcotics laws do not regulate these products. Source: EMCDDA, 2012.	Emergency care hospitals admissions for intoxication involving multiple or unknown substances	Fatal overdoses involving NPS (alone or in combination)
Czech Republic	Narcotic drugs or psychotropic substancesuncovered by the UN Conventions which, because of the extent of their abuse or because they pose a direct or indirect threat to health, require specific regulation. Source: Government Regulation No. 463/2013 Coll., on the lists of addictive substances	Hospitalizations for drug intoxication in emergency care hospitals involving other and unspecified drugs (T40.4, T40.6, T40.9)	Fatal drug overdoses associated with other and unspecified drugs
Portugal	Substances not specifically regulated and controlled under specific legislation which, in pure form or in a preparation, may pose a threat to public health comparable to the substances covered by that legislation, endangering life or health and physical integrity, due to their effects on the central nervous system, may induce significant changes in motor function and mental functions, including reasoning, critical judgement and behaviour, often with states of delirium, hallucinations or extreme euphoria, and can cause addiction and, in some cases, produce lasting or even permanent damage to the health of consumers. Source: Decree-law 54/2013	Intoxications involving addictive substances: other and unknown drugs	Deaths by overdose associated with synthetic drugs
Germany	Substances or substances preparations not listed in the Narcotic Drugs Act that pose a considerable health risk, especially for adolescents and young adults. Source: 2016 German New Psychoactive Substances Act (NpSG)	NPS-related mono & polydrug poisonings	NPS-related deaths (mono & polydrug use)
Belgium	New generation of psychoactive substances or "drugs" (poisonous, soporific, narcotic, psychotropic, disinfectant, or antiseptic substances and substances that can be used for the illicit manufacture of narcotic and psychotropic substances) constituting a growing threat to public health. Source: Royal Decree of 6 September 2017	Telephone inquiries received at the Poison Centre involving NPS and unknown substances	NPS-related deaths
Poland	Any substance of natural or synthetic origin in any physical state or a product, plant, mushroom or part thereof, containing such a substance used instead or for the same purpose as a narcotic drug or psychotropic substance, whose manufacture and commercialisation are not regulated by separate provisions. Source: Act amending the Act on Counteracting Drug Addiction and the Act on State Sanitary Inspection, 2010	Likely medical interventions induced by new psychoactive substances	NPS-induced deaths
England & Wales	"Psychoactive substance" means any substance which (a) is capable of producing a psychoactive effect in a person who consumes it, and (b) is not an exempted substance. A substance produces a psychoactive effect in a person if, by stimulating or depressing the person's central nervous system, it affects the person's mental functioning or emotional state; and references to a substance's psychoactive effects are to be read accordingly. Source: Psychoactive Substances Act 2016	Patients admitted to hospital by poisoning involving other and unspecified narcotics (primary diagnosis)	Deaths mentioning specific substances on the death certificate: new psychoactive substances
Scotland		Drug-related general acute stay *involving sedative/hypnotic (incl. includes new or unlicensed benzodiazepines)	Drug-related deaths (ONS 'wide' definition) involving NPS

Appendix 2

Table A2

Table A2
Sources of data.

Country	Legal instrumentsWebsite	NPS prevalence of use	NPS-related poisoning/intoxications	NPS-related deaths
The Netherlands	Wetten Overheid wetten.overheid.nl	Statistics Netherlands (CBS) Health Survey | Lifestyle Monitor	Drugs Information and Monitoring System (DIMS) | Drugs Informatie en Monitoring Systeem (DIMS) Dutch Poisons Information Centre (DPIC) | National Vergiftigingen Informatie Centrum (NVIC)	Netherlands Forensic Institute (NFI) | Nederlands Forensische Instituut (NFI)
Ireland	electronic Irish Statute Book (eISB) irishstatutebook.ie	Drug prevalence survey of households, Regional Drug and Alcohol Task Force (RDATF)	HIPE, Healthcare Pricing Office	National Drug-Related Deaths Index (NDRDI) - Health Research Board
France	Légifrance legifrance.gouv.fr	Health Barometer | Baromètre de Santé	Oscour Network, Public Health France	Deaths Related to Medecines and Substance Abuse | Décès en Relation avec l'Abus de Médicaments Et de Substances (DRAMES)
Czech Republic	Ministerstvo Zdravotnictvi Ceske Republiky mzcr.cz	Omnibus surveys Prevalence of Drug Use in the Population PPM	Institute of Health Information and Statistics of the Czech Republic | Ústav zdravotnických informací a statistiky ČR	Institute of Health Information and Statistics of the Czech Republic | Ústav zdravotnických informací a statistiky ČR
Portugal	Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências (SICAD) sicad.pt Diário da República Eletrónico dre.pt	National Drug Survey | Inquérito Nacional ao Consumo de Substâncias Psicoativas na População Geral (INPG)	Poison Information centre | Centro de Informação Antivenenos (CIAV)	Special Mortality Register - National Institute of Legal Medicine and Forensic Science | Registros específicos de mortalidade - Instituto Nacional de Medicina Legal e Ciências Forenses
Germany	Bundesministerium für Gesundheit bundesgesundheitsministerium.de	ESA Epidemiological Survey of Substance Abuse | Epidemiologische Suchtsurvey (ESA)	Phar-Mon NPS project & Poison information centre (GIZ)	Federal Criminal Police Office (Bundeskriminalamt, BKA)
Belgium	Belgisch Staatsblad - Moniteur Belge ejustice.just.fgov.be	National Health Survey | Enquête de Santé	Belgian National Poison Centre | Centre Belge Antipoison	General Mortality Register. Belgium Early Warning System on Drugs
Poland	National Bureau for Drug Prevention kbpn.gov.pl European Judicial Training Network (EJTN) ejtn.eu	CBOS Foundation& CINN KBPN population survey CBOS Foundation & CINN KBPN final grade school survey CINN KBPN survey	Poisonings Control Centre, General Sanitary Inspectorate	Poisonings Control Centre, General Sanitary Inspectorate
England & Wales	The National Archives legislation.gov.uk	Crime Survey of England and Wales	The Health and Social Care Information Centre, Hospital Episode Statistics for England	Office for National Statistics
Scotland		Scottish Crime and Justice Survey	NHS Services Scotland - National Statistics	National Records of Scotland

Appendix 3

Table A3

Table A3
List of abbreviations.

Abbreviation	Definition
2C-B	4-Bromo-2,5-dimethoxyphenethylamine
4-FA	4-Fluoroamphetamine
4-MA	1-(4-methylphenyl)propan-2-amine
BZP	Benzylpiperazine
GHB	Gamma-hydroxybutyrate
JWH-18	(1- pentyl- 1H- indol- 3- yl)- 1- naphthalenyl- methanone
NBOMe	25I-NBOMe (2C-I-NBOMe, BOM-CI, Cimbi-5) 25B-NBOMe (2C-B-NBOMe, 25B, Cimbi-36) 25C–NBOMe (2C–C-NBOMe, 25C, N-Bomb, Cimbi-82) 2C-BCB-NBOMe (2-TCB-NBOMe)
PMMA	1-(4-methoxyphenyl)−2-methylaminopropane
U-47,700	Trans-3,4-dichloro-N-[2- (*dimethylamino*)*cyclohexyl*]-N-methyl- benzamide
ANSM	National Agency for Medicines Security | Agence nationale de sécurité du médicament et des produits de santé
BEWSD	Belgian Early Warning System on Drugs
BtMG	German Federal Narcotics Act | Betäubungsmittelgesetz
CIAV	Poison Information Centre | Centro de Informação Antivenenos
DIMS	Dutch Drugs Information and Monitoring System
DPIC	Dutch Poisons Information Centre
DRAMES	Deaths Related to Medecines and Substance Abuse | Décès en Relation avec l'Abus de Médicaments Et de Substances
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
GIZ	Poison information centre | Giftinformationszentrale
HIPE	Hospital In-Patient Enquiry
MDA	Misuse of Drugs Act
NPS	Novel Psychoactive Substances
NpSG	New Psychoactive Substances Act
NSO	Novel Synthetic Opioids
PSA	Psychoactive Substances Act
SCRAs	Synthetic Cannabinoid Receptor Agonists
SICAD	General Directorate for Intervention on Addictive Behaviours and Dependencies | Serviço de Intervenção nos Comportamentos Aditivos e nas Dependências

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