Emerging Trends in Drugs, Addictions, and Health 3 (2023) 100053

Contents lists available at ScienceDirect

Emerging Trends in Drugs, Addictions, and Health

journal homepage: www.elsevier.com/locate/etdah

Analysing the use trends of new psychoactive substances using wastewater-based epidemiology in Europe: A systematic review

Gabriel Gatica-Bahamonde [a,b,c,#], Elizabeth Alexandra Godynyuk [a,#], Jessica Neicun [a], Emmert Roberts [f], Mehmet Mikail Tangerli [a], Robin van Kessel [a,g], Katarzyna Czabanowska [a,#], Keith Humphreys [d,#], Andres Roman-Urrestarazu [a,b,e,#,*]

[a] Department of International Health, Care and Public Health Research Institute (CAPHRI), Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands
[b] Departamento de Salud Mental y Psiquiatría, Universidad de La Frontera, Temuco, Chile
[c] Departamento de Salud Pública, Universidad de La Frontera, Temuco, Chile
[d] Veterans Affairs Health Care System, Palo Alto, CA, USA
[e] Department of Psychiatry, University of Cambridge, Cambridge, United Kingdom
[f] Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, California, USA
[g] LSE Health, Department of Health Policy, London School of Economics and Political Science, London, United Kingdom

ARTICLE INFO

Keywords:
New psychoactive substance
Wastewater-based epidemiology
Metabolite presence
Europe
Public health

ABSTRACT

Background and Aims: New psychoactive substances (NPS) pose challenges not only due to their harms to users but also because they are difficult to monitor with traditional epidemiologic methods. Wastewater-based epidemiology (WBE) offers a reliable method to assess drug-taking habits in different geographical settings and their evolution over time. The aim of this systematic review was to examine NPS preferences and trends across Europe.

Methods: We searched electronic databases between September 5th to 30th, 2022, included OVID/Embase, PubMed, Scopus, and Web of Knowledge. Key search terms focused on NPS, WBE, prevalence, and geographic Europe. 18 articles were included in the systematic review. All studies were WBE studies, with 17 studies collecting samples from wastewater treatment plants, one collecting from pissoirs. Due to heterogeneity across studies, a meta-analysis was not performed.

Results: Literature reviewed in this study showed a trend towards stimulant-type NPS use, with the United Kingdom showing highest detection frequency. The most detected chemical class of NPS were synthetic cathinones. Southern and Western Europe showed the largest variety of NPS detected. Metabolite detection ranged extensively across countries.

Conclusion: This is the first systematic review to address types of new psychoactive substances present in wastewater in Europe. Gaps in literature point to a need for standardization in wastewater-based epidemiology so that drug policies and public health policies, including drug and harm reduction services, can be targeted to those NPS that are most widely used.

Introduction

In the European Union, 83 million (28.9%) adults between 15 and 64 years of age are estimated to have tried an illicit drug during their lifespan (European Monitoring Centre for Drugs and Drug Addiction 2021). Despite an earlier report published in December 2020 detailing disturbances in drug use, associated trends in drug preference, and drug trafficking (European Monitoring Centre for Drugs and Drug Addiction 2020), the illicit drug market continues to evolve. The complexity of available drugs is rapidly rising, especially considering an increasing

Declarations of competing interest: The Authors have declared there are no competing interests.Primary funding: Harkness Fellowship to ARU and ER.
* Corresponding author at: Autism Research center - ARC, University of Cambridge, Douglas House, 18b Trumpington Road, Cambridge, CB2 8AH, United Kingdom
E-mail address: aer56@medschl.cam.ac.uk (A. Roman-Urrestarazu).
# These authors contributed equally to this work.

https://doi.org/10.1016/j.etdah.2023.100053
Received 17 March 2023; Received in revised form 28 June 2023; Accepted 16 August 2023
Available online 21 August 2023

number of new psychoactive substances that were previously unknown and have been mostly identified through drug discussion forums (Catalani et al., 2021).

New Psychoactive Substances (NPS) are defined as psychoactive substances uncovered under international control through the Single convention on Narcotic Drugs of 1961 or the Convention on Psychotropic Substances of 1971 (United Nations Office on Drugs and Crime 2013). This includes synthetic cannabinoids (SC), opioids, 'new' benzodiazepines, hallucinogens, stimulants, and dissociatives (European Monitoring Centre for Drugs and Drug Addiction 2020). Recreational use, self-medication, and cognitive enhancement are the most reported reasons for NPS consumption (Soussan et al., 2018), with these drugs typically presented as 'legal' alternatives to traditional illicit drugs that mimic their effects (Catalani et al., 2021; Soussan et al., 2018). As of 2020, the European Monitoring center for Drugs and Drug Addiction (EMCDDA) monitored 830 NPS (European Monitoring Centre for Drugs and Drug Addiction 2021), while web crawlers such as NPSfinder® have identified additional substances that had not been formally reported to the EMCDDA, thus the actual number of NPS available is difficult to determine (Catalani et al., 2021).

NPS are particularly challenging as their availability and constant modifications make it difficult to control and anticipate trends in supply and demand (Khaled et al., 2016). This is further complicated by the uncertainty of the drug's effects on users, as metabolic outcomes, physiological effects, and drug-drug interactions are typically unknown, with potentially severe negative consequences (Zawilska and Andrzejczak, 2015). Molecular alterations of NPS also provide a means to circumvent legislative frameworks and detection in traditional drug tests. Thus, the European Parliament and Council of the European Union have already highlighted their potential in creating cross-border threats to health (European Parliament and Council of the European Union 2013).

Acute poisonings resulting from use of NPS can occur amongst drug-using populations (Moritz et al., 2018; Iwersen-Bergmann et al., 2019) Between 2014–2017, 9% of acute toxicity presentations across 21 countries were attributed to NPS (European Monitoring Centre for Drugs and Drug Addiction 2020). Acute poisonings may suddenly exert pressure on multiple healthcare professionals and healthcare systems. Difficulties in identifying NPS in a timely manner makes clinical management challenging as healthcare professionals do not immediately known what has been ingested and describe overall limited knowledge of NPS (Pirona et al., 2017). Moreover, traditional drug screenings may not detect many NPS (Graziano et al., 2019), thus putting individuals at further risk to health due to potential barriers in access to appropriate treatment in the case of poisoning (Van Hout et al., 2018). This is particularly worrisome, especially when users are unaware of the actual composition of the drug, whether ingested willingly or unwillingly (Van Hout et al., 2018). More sophisticated and time-consuming screenings may elucidate and highlight currently circulating NPS as a mechanism to tackle and anticipate trends in drug consumption and health harms (Helander et al., 2020; Felvinczi et al., 2020). Despite obstacles, recent initiatives have provided rapid screening methods for NPS and illicit drugs, offering more timely results (Larabi et al., 2019).

As drug dependence, poor mental health outcomes, and drug-related infectious diseases already pose challenges for public health policy responses (Van Hout et al., 2018), evidence shows that more adverse outcomes may be attributed to NPS use when compared to traditional illicit drugs (Van Hout et al., 2018; Helander et al., 2020). A study analysing mental health outcomes of SC-users compared to natural cannabis (NC) users through psychometric measure outcomes, showed higher scores for drug abuse, sleep problems, and hypomanic symptoms (Mensen et al., 2019). Furthermore, SC-users scored significantly higher in somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoia, and psychoticism (Mensen et al., 2019). Another study found an increase in impulsivity and lower self-control in NPS-users taking 'club drugs' (Savulich et al., 2021), of which some participants were seeking treatment for problematic use. Impulsivity among NPS-users may also lead to damage to third parties. Driving under the influence of drugs is a significant public health concern, particularly if traditional screening systems do not identify any NPS with further analysis being required to determine whether a NPS has been ingested (Richeval et al., 2018). Finally, NPS have recently been attributed to increasing prevalence of Hepatitis C and HIV among people who inject drugs (McAuley et al., 2019; Giese et al., 2015), each presenting their own negative health outcomes and complications.

To understand prevalence of drug use, convenience sample surveys, toxicology reports, and police seizure data may provide snapshots of drug consumption trends, availability, and toxicity (Iwersen-Bergmann et al., 2019; Stephenson, 2014; Corkery et al., 2020), though all these tools present serious limitations. Among those who participate in surveys or questionnaires, typical NPS-user profiles generally fall under the following categories: marginalized users receiving treatment (including homeless people), psychonauts, prison populations, and nightlife recreational users (Van Hout et al., 2018; Felvinczi et al., 2020; Werse et al., 2019). Marginalized people who use drugs are typically recruited through harm reduction services (HRS), drug treatment facilities or shelters of larger cities (Werse et al., 2019). Although undocumented residents, people who may not be currently seeking HRS, those who are not able to access treatment due to geographic location, or those not wishing to participate in studies may be missed by these studies (Reuter et al., 2021). Further studies have also shown that users often report purchasing NPS either through the internet, from surface websites or crypto-markets, or through other sources such as street dealers (Catalani et al., 2023; Corkery et al., 2020; Werse et al., 2019; Sutherland et al., 2017). Despite legislative attempts to reduce NPS online availability (Stephenson, 2014), alternative methods may be used to obtain them offline (Werse et al., 2019). Overall, convenience sampling provides a limited description of current trends and availability of NPS, with prevalence of NPS use likely to be over-represented among communities reached by this sampling method. As risk assessment on NPS is still very limited (Shafi et al., 2017), with shifting trends in drug preference among different communities being observed, better anticipation for treatment demand is required.

In this frame, Wastewater-Based Epidemiology (WBE) provides an alternative anonymous assessment of drug-taking habits through the analysis of drug residues (drug metabolites excreted in urine) in wastewater, enabling a quantitative measure of the loads of a substance released in a specific geographic area (Zuccato et al., 2008). Based on its methodological characteristics, WBE provides a spatial and temporal understanding of trends in illicit drug use, which allows it to be a complementary approach to other traditional epidemiological approaches to drug use (Gent and Paul, 2021; Escolà Casas et al., 2021). Additionally, WBE studies are typically faster and more accessible than population-based studies, as samples are collected in wastewater treatment plants (WWTP) (Feng et al., 2018). In 2011, (Thomas et al., 2012) published the results of the first international assessment of WBE in 19 European countries. In a subsequent important study, (González-Mariño et al., 2020) reported spatial and temporal trends in drug use through wastewater analysis over a 7-years period (Mensen et al., 2019). The study analysed the presence of 4 stimulant drugs: Cocaine (through its main metabolite Benzoylecgonine), Amphetamine, Methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA). The authors reported intraregional and intercontinental differences in the substances detected. Based on the growing reliability of wastewater analysis, the main aim of this systematic review is to identify patterns of NPS use and trends over time though a systematic review of available scientific literature on WBE studies conducted in Europe during the last decade. Results from this systematic review are intended to provide additional evidence on trends in NPS use across Europe thus supporting more comprehensive public health responses. Study findings will be discussed

Table 1
Search terms and criteria for the development of a search strategy.

	Criteria	Search Terms
Population	New Psychoactive Substance/ Designer drug consumption trends	'New Psychoactive Substance' OR 'New Psychoactive Substance' OR 'Designer drug'
'Intervention'	Drug Prevalence (ng/L or mg/ day/1000 inhabitants)	Prevalence OR Epidemiology OR monitor* OR Surveillance
Location	Europe	Europe OR Europ* OR EU OR European OR European Union
Outcome	Prevalence of NPS in wastewater, detected in wastewater treatment plants or urinals	Wastewater Analysis OR Wastewater epidemiology OR 'WBE' OR Wastewater

Table 2
Inclusion and exclusion criteria for articles.

Inclusion criteria	Exclusion criteria
1. English language text	1. Text in a language other than English
2. Text accessible through Maastricht University	2. Text not accessible through Maastricht University
3. Publication refers to NPS or Designer Drugs	3. Publication refers only to traditional illicit drugs
4. Publication is not a review	4. Publication is a review
5. Publication is peer-reviewed	5. Publication is not peer-reviewed
6. NPS category, either psychoactive or chemical, is provided	6. No mention of NPS name or category
7. Wastewater analyses performed in Europe	7. Wastewater analyses performed outside of Europe only

in the light of data on hospital admissions, toxicology reports, and cross-sectional surveys.

Methods

A systematic review was performed following a protocol conducted prior to the start of the study. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and registered on PROSPERO (Registration: 360,901) (Page et al., 2021).

Search strategy

A systematic search of literature was performed between the 5th and 30th of September 2022, using a search strategy that was developed initially by EAG and followed up by ARU and GGB. We searched four databases including: PubMed, Scopus, OVID/EMBASE, and Web of Science (Core Collection). Search terms were based on the population type, exposure or 'intervention', location, and outcome, as shown in Table 1. A detailed summary of the search strategy and terms used in each database can be found in the Supplementary material (S1).

Following the systematic search, the references were exported to an EndNote database (EndNote version X7.7.1).

Eligibility and selection criteria

The inclusion criteria are shown in Table 2.

After completion of the systematic search and elimination of duplicates, two researchers (EAG and MMT) independently performed the screening phase suggested by the PRISMA criteria (Page et al., 2021) (Fig. 1). Selection of articles was done in an independent two-step process carried out by three reviewers (EAG, GGB and MMT). Titles and abstracts were firstly assessed, followed by full texts. Disagreements were resolved through discussion. A Kappa's Cohen coefficient was also calculated.

Data collection and synthesis

Data extraction was carried out by three reviewers (EAG, GGB and ARU). A summary of the studies was extracted and synthesized, including the year of study, locations, study period, estimated population size wastewater treatment plants treated, number of wastewater treatment plants, demographics, length and/or number of samples collected, and analysis used to confirm presence of NPS. Further descriptive outcomes were NPS name, NPS psychoactive and chemical class, NPS loads found in wastewater, level of confirmation, and trends if relevant, were extracted.

Bias assessment

Risk of bias between wastewater studies were assessed using the quality assessment checklist for prevalence studies (Hoy et al., 2012). Outcomes were then synthesized and reviewed to determine risk of bias amongst studies included in the review (see S2). The tool utilizes two domains, internal and external validity, across 10 questions, for a bias score established between low- to medium- to high-risk.

Of the 18 articles selected for review, 11 were rated low-risk, five were rated moderate-risk, and two were rated high-risk of bias. The high-risk groups were qualitative studies, of which no prevalence rates could be extracted. No quantitative studies were rated as high-risk of bias. Three quantitative and two qualitative studies were rated as moderate-risk studies. Internal validity was mostly moderate- or high-risk in this group, where sampling was not representative of the total population, either due to the use of pissoirs, providing a limited scope of individuals, and/or because data collection was not similar in all cases. Finally, 11 quantitative studies were rated as low risk. These studies provided adequate internal and external validity outcomes. Also, data collection methods differed between countries due to the wastewater collection methods. Overall, the results from the critical appraisal may indicate a lower risk of bias, with limitations.

Results

The first phase of screening yielded 19 articles, and the second phase resulted in 18 articles selected for review. A total of 18 studies were finally assessed as eligible for review (Fig. 1). Agreement between reviewers was rated substantial, at 91.84% (Cohen's kappa = 0.82). A summary description of methodologies used in reviewed studies can be found in Supplementary material (S3). Publication dates ranged from 2014 to 2021, and samples were collected between 2012 and 2020. Two papers did not provide a sample collection timeframe (I González-Mariño et al., 2016; Celma et al., 2019). As shown in Table 3, a total of 21 European countries were investigated: each country appeared in between 1 and 7 studies (S4), with the United Kingdom appearing most often. One study did not provide locations for samples collection, specifying it was a European-wide study (Celma et al., 2019). Samples ranged from one to 37 cities. Most articles reviewed did not overlap in study timeframe. An overlap between two studies regarding timeframe and geographic location (Salgueiro-González et al., 2019; Castiglioni et al., 2021) was presumed, yet different outcomes were found, thus enhancing overall results. Studies ranged in length of data collection, from one day of 24-hour composite sampling, period-sampling either once per week for a few weeks, or for multiple consecutive days across several months.

Population size of cities varied between studies, ranging from 19,800 to 6000,000 habitants. Three studies covering a single country provided a population size coverage estimate of 12.8% (Bijlsma et al., 2021), 20% (Brandeburová et al., 2020), and 40% (Kankaanpää et al., 2014), respectively. Six studies did not provide a population estimate or census (I González-Mariño et al., 2016; Celma et al., 2019; Salgueiro-González et al., 2019; Bade et al., 2017; Styszko et al., 2016; Archer et al., 2014). All studies, except for one which focused on male nightlife drug use

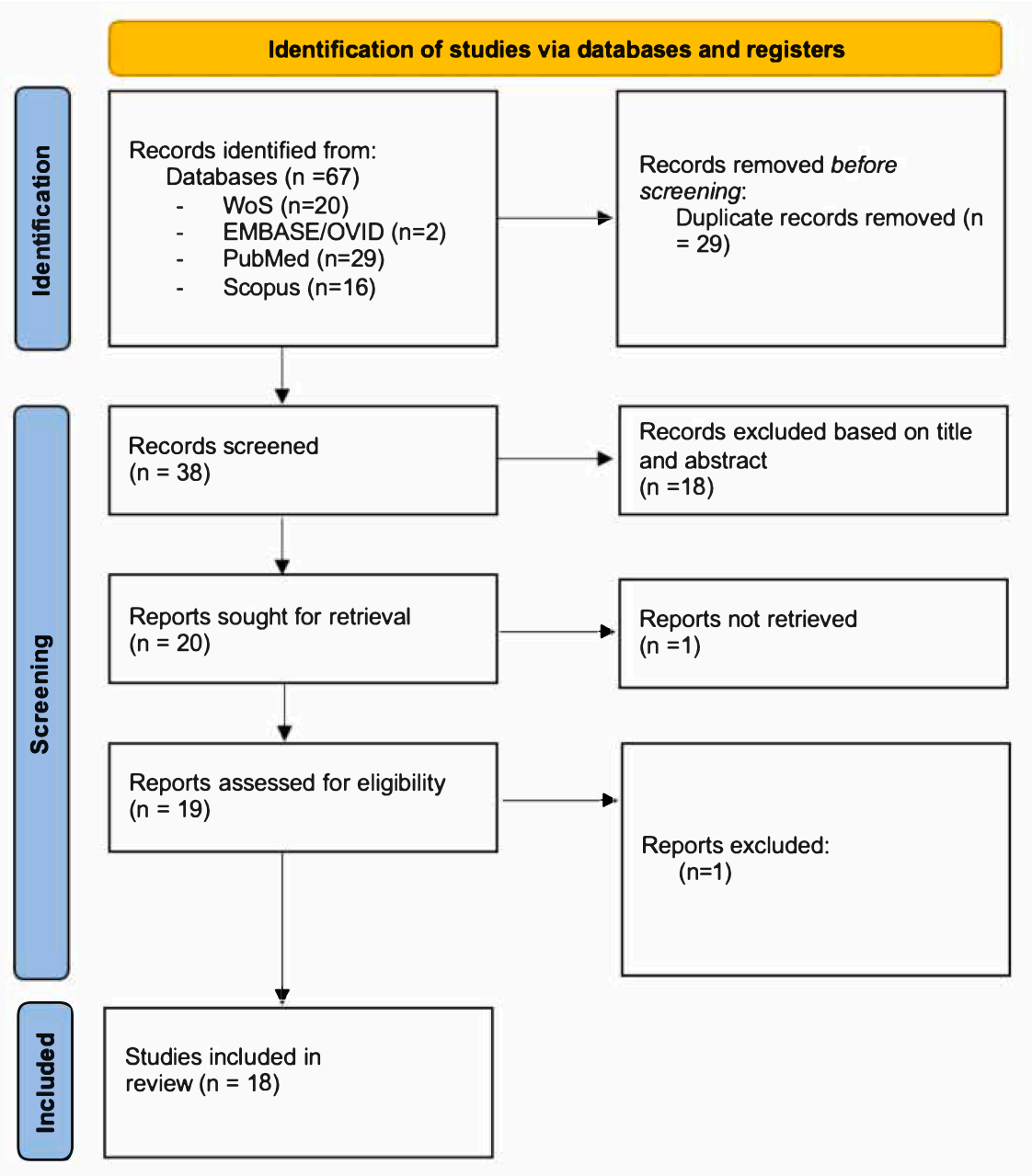

Fig. 1. Prisma 2020 Flow diagram for systematic reviews.

Table 3
European countries under study by region.

Northern Europe (NE)	Southern Europe (SE)	Eastern Europe (EE)	Western Europe (WE)
Denmark	Greece	Bosnia-Herzegovina	Belgium
Finland	Italy	Bulgaria	Germany
Ireland	Portugal	Poland	Switzerland
Norway	Slovakia	Romania	The Netherlands
United Kingdom	Spain	Serbia	
		Slovenia	
		Ukraine	

patterns (Archer et al., 2014), focused on the general population. Within these studies, four also examined festival wastewater (Brandeburová et al., 2020; Bijlsma et al., 2020; Causanilles et al., 2017; Kinyua et al., 2015), and one examined wastewater at a popular holiday destination in the Netherlands (Bade et al., 2021).

Finally, to determine primary outcomes, a range of analyses were used to identify NPS from WBE. Common methods to extract data include separation techniques coupled with structural identification. In quantification studies, the most common method described was liquid chromatography – mass spectrometry (LC-MS/MS), appearing in five studies (Bijlsma et al., 2021; Brandeburová et al., 2020; Bijlsma et al., 2020; Bade et al., 2021; Rice et al., 2020), followed by high performance LC-MS/MS (HPLC-MS/MS) used in three studies (Castiglioni et al., 2021; I González-Mariño et al., 2016; Sulej-Suchomska et al., 2020), ultra-high performance LC-MS/MS (UHPLC-MS/MS) used in three studies (Celma et al., 2019; Kankaanpää et al., 2014; Bade et al., 2017), quadrupole time-of-flight LC-MS/MS (LC-QTOF-MS/MS) used in two studies (Styszko et al., 2016; Diamanti et al., 2019), LC-Electrospray Ionization-MS (LC-ESI-MS/MS) used in a single study (Kinyua et al., 2015), and micro-LC-MS/MS also used in one study (Celma et al., 2019).

Table 4
Summary of the included studies.

Reference (Number)	Year	Study time frame	Location	Study Type	Sample	# NPS tested	Length or numbers of collection/ # WWTP	Sample group	Population size (estimate)	Demographics	Primary Outcome	Analysis	Time/Flow
36	2016	Unknown	Italy	Wastewater Analysis	4 cities: Milan, Bologna, Turin, Perugia	52	24-hour composite samples 4 WWTP 42 wastewater samples	General Population	Unknown (not given)	General population	Qualitative measure	LC—HRMS HPLC-LTQ-Orbitrap-HRMS	Volume-proportional Time-proportional
37	2019	Unknown	Europe	Wastewater Analysis	8 WWTPs	15	24-hour composite samples (weekends 1:1:1 ration) 8 WWTP	General Population	Unknown (not given)	General population	Concentration (ng/L)	UHPLC-MS/MS μLC-MS/MS	Not given
38	2019	2016–2017	Bosnia & Herzegovina, Bulgaria, Italy, Ireland, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Switzerland, The Netherlands, Ukraine, UK, Germany	Wastewater Analysis	22 countries, 37 cities	197	24 h 15 countries (26 cities) - 2016; 7 countries (11 cities) - 2017	General Population	Unknown (not given)	General population	Qualitative measure	LC—HRMS	Time-proportional Flow-proportional
39	2021	2016–2017	Bosnia-Herzegovina, Bulgaria, Ireland, Italy, The Netherlands, Italy, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Switzerland, Ukraine, UK	Wastewater Analysis	14 European countries 22 cities	30	24 h, 3-days over the weekend (March-May 2016), 7-days over the week (March-May 2017 + October (1 city)) 15 countries (22 cities) 23 WWTP	General Population	Bosnia-Herzegovina - N/A Bulgaria - 575,178 Ireland - N/A Italy - 1140,000 1080,000; 459,650; 500,000 The Netherlands - 300,000 Poland - 480,000, 465,000 Portugal -150,000 Romania - 65,000; 367,000; 1850,000 Serbia - 30,000 Slovakia -	General population	Excreted mass load (mg/day/1000)	SPE-HPLC-MS/MS	Flow-proportional

(*continued on next page*)

Table 4 (*continued*)

Reference (Number)	Year	Study time frame	Location	Study Type	Sample	# NPS tested	Length or numbers of collection/ # WWTP	Sample group	Population size (estimate)	Demographics	Primary Outcome	Analysis	Time/Flow
									450,000; 120,000; 30,000; 89,600 Slovenia - 26,908, 51,635, 57,085 Switzerland - 103,561 Ukraine - N/A United Kingdom - 886,650				
40	2021	2018	Spain	Wastewater Analysis	13 Spanish cities: Barcelona, Bilbao, Castellon, Guadalajara, Lleida, Madrid-1, Madrid-2, Mostoles, Palma de Mallorca, Reus, Santiago de Compostela, Tarragona, Toledo, Valencia	17	7 days (March-June) 17 WWTP	General Population	6000,000 (12.8% of population)	30–100% of population coverage	Excreted mass load (mg/d/1000)	LC-MS/MS	Time-proportional (14+1) Flow-proportional (European Monitoring Centre for Drugs and Drug Addiction 2020)
41	2020	2017–2018	Slovakia	Wastewater Analysis Urine samples	Bratislava central, Bratislava Petržalka, Košice, Prešov, Trenčín, Piešťany, Nitra, Komárno, Trnava, Žilina	30	24-hour composite samples 1–6-day sampling period 7 WWTP (3 cities), 3 music festivals	General Population Festival	20% of Slovakia's population Košice - 215,000 Prešov - 100,000 Trenčín - 47,000 Piešťany - 30,000 Nitra - 80,000 Komárno - 30,000 Trnava - 89,600	General population Music festivals	Concentration (ng/L) Excreted mass load (mg/day/1000)	LC-MS/MS	Time-proportional
42	2014	2012	Finland	Wastewater Analysis	Espoo, Helsinki, Jyväskylä, Kuopio, Lahti, Lappeenranta, Oulu, Rovaniemi, Tampere and Turku	2	24-hour composite samples 10 WWTP 5–7x samples consecutive	General Population	40% Finnish population Helsinki: 800,000 Espoo: 310,000 Turku: 275,000 Tampere: 200,000 Jyväskylä: 150,000	General population	Excreted mass load (mg/day/1000)	UHPLC-MS/MS	Time-proportional Volume-proportional

(*continued on next page*)

Table 4 (*continued*)

Reference (Number)	Year	Study time frame	Location	Study Type	Sample	# NPS tested	Length or numbers of collection/ # WWTP	Sample group	Population size (estimate)	Demographics	Primary Outcome	Analysis	Time/Flow
									Kuopio: 80,000 Lahti: 100,000 Lappeenranta: 60,000 Oulu: 147,350 Rovaniemi: 58,000				
43	2017	2015	Switzerland, Denmark, Norway, Spain, Italy, Belgium, The Netherlands, UK	Wastewater Analysis	8 countries 8 European cities	10	March 24-hour composite samples Weekend & Weekday Unknown	General Population	Unknown (not given)	General population	Concentration (ng/L)	UHPLC-MS/MS	Flow-proportional
44	2016	2012	Poland	Wastewater Analysis	Krakow, Poland	4	4 weeks 1 WWTP 4 samples collected (1x week)	GeneralPopulation	Unknown (not given)	General population	Concentration (ng/L)	LC-QTOF-MS/MS	Flow-proportional
45	2014	2012	UK	Wastewater Analysis Urine samples	12 4-bay urinals in London	Unknown	6 months (July - December) Sampled every 1st Saturday after 12 h 6 samples, 72 samples total	Nightlife	Unknown (not given)	Men close to nighttime economy	Frequency of drugs detected	LC—HRMS UPLC—Orbitrap-HRMS	Not given
46	2020	2015–2018	UK, Belgium, Norway, Portugal, Serbia, Spain	Wastewater Analysis Urine samples	7 countries 6 European festivals	197	2–14 festival days; 3–4 non-festival days 36 wastewater samples (3 WWTP; 24 h, Portugal, Serbia, Spain) + 56 pooled urine samples (34 urinals/ toilets; 12 h; UK, Belgium, Norway)	General Population Festival	465.000	Festival-goers General population (Urine samples -2/3 male urinals, 1 male/female portable toilet)	Concentration (micorgram/L) Excreted mass load (mg/d/ 1000; g/day) Qualitative measure	LC-MS/MS LC—HRMS	Time-proportional
47	2017	2012 2014	The Netherlands	Wastewater Analysis	Amsterdam, The Netherlands	560	Summer 2012 & Summer 2014 (24hr composite samples Thursday-Sunday) 1	General Population	769,000 300,000 visitors for the festival	Festival General population	Qualitative measure	LC—HRMS LC-QTOF-MS/MS Orbitrap-LC/MS	Flow-proportional

(*continued on next page*)

Table 4 (*continued*)

Reference (Number)	Year	Study time frame	Location	Study Type	Sample	# NPS tested	Length or numbers of collection/ # WWTP	Sample group	Population size (estimate)	Demographics	Primary Outcome	Analysis	Time/Flow
							WWTP 8 composite samples						
48	2015	2013–2014	Belgium, Switzerland	Wastewater Analysis	2 countries 8 cities	7	24-hour composite samples 6 WWTP (1 CH; 7 BE)	General Population Festival	Zurich (CH) - 410,000 Antwerp-Noord (BE) - 94,500 Boechout (BE) - 19,800 Ruisbroek (BE) - 36,000 Zele (BE) - 20,700 Ninove (BE) - 31,500 Antwerp-Zuid (BE) - 171,000 Antwerp-Deurne (BE) - 193,500	General population Festival goers in Zurich	Concentration (ng/L)	LC-ESI-MS/MS	Time-proportional Volume-proportional
49	2021	2019–2020	Spain, Italy, The Netherlands, Norway (Other cities not considered)	Wastewater Analysis	4 European cities (1 site each)	26	7–15 days (samples): 11 days - Spain, Italy 7 day - The Netherlands 5 multi-day samples (Dec. 20–22, Dec 23–26, Dec 27–29, Dec 30-Jan 1, Jan 3–5), 1 daily sample Jan 2 - Norway 4 WWTP	General Population Census	Spain - 170,888 Italy - 1122,501 NL - 769,000 Norway - 624,642	General population Holiday destination - (NL)	Excreted mass load (mg/d/ 1000) Qualitative measure	LC-MS/MS LC—HRMS	Flow-proportional
50	2020	2014–2018	UK	Wastewater Analysis	1 WWTP	1	1 week over 5 years 1 WWTP	General Population	886.650	General population	Excreted mass load (mg/day/ 1000)	LC-MS/MS	Time-proportional
51	2016	2014–2015	Italy, Norway, Spain, UK	Wastewater Analysis	8 cities 4 countries	17	24-hour composite samples 3–10-day sampling period 8 WWTP	General Population Event (Italy)	Florence (IT): 204,000 Bologna (IT): 500,000 Turin (IT): 1370,000 Perugia (IT): 47,800 Milan (IT): 1100,000 Oslo (NO): 580,639 Santiago de Compostela	General population	Concentration (ng/L) Excreted mass load (mg/day/ 1000)	SPE-HPLC-MS/ MS	Time-proportional Volume-proportional

(*continued on next page*)

Table 4 (*continued*)

Reference (Number)	Year	Study time frame	Location	Study Type	Sample	# NPS tested	Length or numbers of collection/ # WWTP	Sample group	Population size (estimate)	Demographics	Primary Outcome	Analysis	Time/Flow
									(ES): 136,500 SW city (UK): 886,650				
52	2020	2015–2016	Poland	Wastewater Analysis	Poznan, Poland	1	7:00–19:00 2 days in 2015 7 consecutive days in 2016 1 WWTP	General Population	1.200.000	General population	Concentration (ng/L)	SPE-HPLC/MS-MS	Time-proportional
53	2019	2015–2018	Greece	Wastewater Analysis	Athens, Greece	729	8 days - 2015, 8 days - 2016, 7 days - 2017, 7 days - 2018 1 WWTP 30 samples	General Population	3.700.000	General population	Excreted mass load (mg/day/1000) Qualitative Measures	LC-QTOF-MS/MS LC—HRMS	Flow-proportional

Qualitative studies used liquid chromatography – high resolution accurate spectrometry (LC—HRMS). Further descriptions can be found in Supplementary material (S3). Finally, studies varied extensively in the number of NPS tested for, from 1 to 729. A summary of the studies included in the analysis can be found in Table 4.

Descriptive summary

All 18 studies were wastewater analysis articles, using quantitative or qualitative methods to estimate NPS use, of which one article describing frequency of NPS identified over time (Archer et al., 2014). Quantitative method outcomes were given either as concentration of NPS in wastewater described in eight articles (Celma et al., 2019; Brandeburová et al., 2020; Bade et al., 2017; Styszko et al., 2016; Bijlsma et al., 2020; Kinyua et al., 2015; Sulej-Suchomska et al., 2020; Diamanti et al., 2019), or excreted mass loads in the population described in nine articles (Castiglioni et al., 2021; Bijlsma et al., 2021; Brandeburová et al., 2020; Kankaanpää et al., 2014; Bijlsma et al., 2020; Bade et al., 2021; Rice et al., 2020; I González-Mariño et al., 2016; Sulej-Suchomska et al., 2020; Diamanti et al., 2019). Three articles used a combination of quantitative and qualitative methods (Bijlsma et al., 2020; Bade et al., 2021; Diamanti et al., 2019). Qualitative methods reported confirmation levels of NPS present in wastewater, with four articles addressing this outcome (Salgueiro-González et al., 2019; Causanilles et al., 2017; Bade et al., 2021; Diamanti et al., 2019). Seventeen studies utilized wastewater analysis by means of data collected from wastewater treatment plants (WWTPs), with data collection ranging from 24-hour composite samples to 56 pooled samples (I González-Mariño et al., 2016; Celma et al., 2019; Salgueiro-González et al., 2019; Castiglioni et al., 2021; Bijlsma et al., 2021; Brandeburová et al., 2020; Kankaanpää et al., 2014; Bade et al., 2017; Styszko et al., 2016; Bijlsma et al., 2020; Causanilles et al., 2017; Kinyua et al., 2015; Bade et al., 2021; Rice et al., 2020; I González-Mariño et al., 2016; Sulej-Suchomska et al., 2020; Diamanti et al., 2019). Two studies included samples collected from pissoirs and toilets (Brandeburová et al., 2020; Bijlsma et al., 2020). One study solely used samples collected from urinals (Archer et al., 2014).

A total of 150 NPS were described, ranging from one to 19 NPS per article (S4), and a total of 66 individual NPS were identified across all studies (S5), with a average of 8 NPS described per study. The most common NPS psychoactive class were stimulants – identified in 18 studies – encompassing 76% total NPS (Fig. 2, A), while synthetic cathinones were the most common chemical class, identified in 17 studies (58% total NPS) (Fig. 2, B). The most common NPS identified was mephedrone, reported in 12 studies (40.1%) (Celma et al., 2019; Castiglioni et al., 2021; Bijlsma et al., 2021; Brandeburová et al., 2020; Bade et al., 2017; Styszko et al., 2016; Archer et al., 2014; Bijlsma et al., 2020; Bade et al., 2021; Rice et al., 2020; I González-Mariño et al., 2016; Sulej-Suchomska et al., 2020).

Further analysis on a country-by-country basis revealed a sum of 150 NPS descriptions (S4), showing an overlap in NPS-taking habits and trends among different regions (S5). Fig. 3 shows the breakdown of NPS psychoactive-class and chemical-class across countries. The country showing the highest stimulant level was the United Kingdom, while Portugal showed the highest level for psychedelics-type NPS. Dissociative-type NPS were most prevalent in Greece (including two NPS of unknown psychoactive class). The country with highest synthetic cathinones level was the United Kingdom, while Greece, Italy, and the Netherlands recorded the highest levels for phenethylamine-type NPS detection. Overall, Greece recorded the largest variety of psychoactive and chemical classes of NPS identified. Mephedrone was the most detected, appearing in 13 countries (see S5). Temporal trends of NPS across countries can be found in Fig. 4.

Spatial and temporal trends were analysed across Europe. Fig. 5 outlines psychoactive and chemical class distributions based on location. Southern Europe reported the widest variety of NPS by chemical

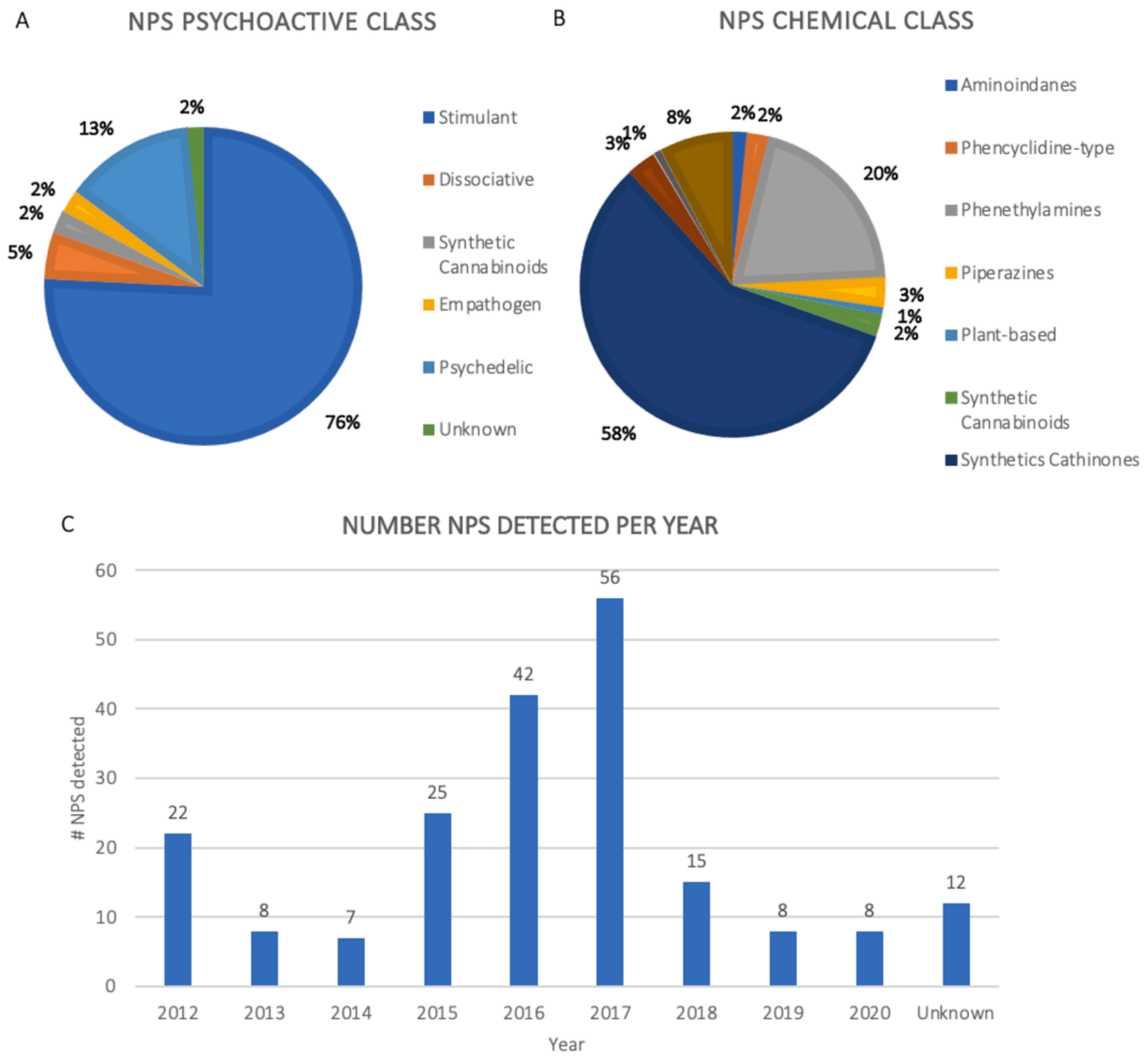

Fig. 2. Frequency of identified NPS. A) breakdown of each psychoactive class found in reviewed articles, out of 100%. Stimulants accounted for 76% of all NPS. B) breakdown of each chemical class found in reviewed articles, out of 100%. Synthetic cathinones accounted for 58% of all NPS. C) Number of NPS identified each year in reviewed articles, showing most detected NPS in 2017. 12 NPS were detected at an unknown period of time.

class (Fig. 6), identifying the largest number of synthetic cathinones, phenethylamines, tryptamines, and the 'other' category across all locations, while Eastern Europe showed the second highest number of phenethylamines. Western Europe recorded the highest number of SC and phencyclidine-type NPS and was the only area to detect amphetamine (in the Netherlands). The UK was the only country to report a plant based NPS. This country also showed the highest number of piperazines and was the only one not to find aminoindanes. In terms of psychoactive class, all locations showed high stimulant-type NPS presence, with Southern and Northern Europe showing the first and second-highest number of psychedelics, respectively. Frequency rates for other chemical classes were low. Finally, Western Europe and Southern Europe showed the highest variety in chemical and psychoactive types of NPS.

Patterns of NPS use

Not all studies provided raw data or quantifiable results, thus only ranges of NPS metabolites detected could be determined for 36 NPS (S6). NPS concentrations and excreted mass loads varied greatly. One study collecting wastewater during festival days reported NPS concentration in micrograms per litter (ug/L) from pooled urine samples, and g/day collected from wastewater samples (Bijlsma et al., 2020). Upon conversion, pooled urine concentrations provided the highest levels of NPS given in ug/L, shown in Table 4. Mephedrone concentration and excreted mass load range was the largest across studies, along with PMA Table 5.

Discussion

The aim of this systematic review was to elucidate preferences and trends in NPS use through WBE across Europe. The most frequently

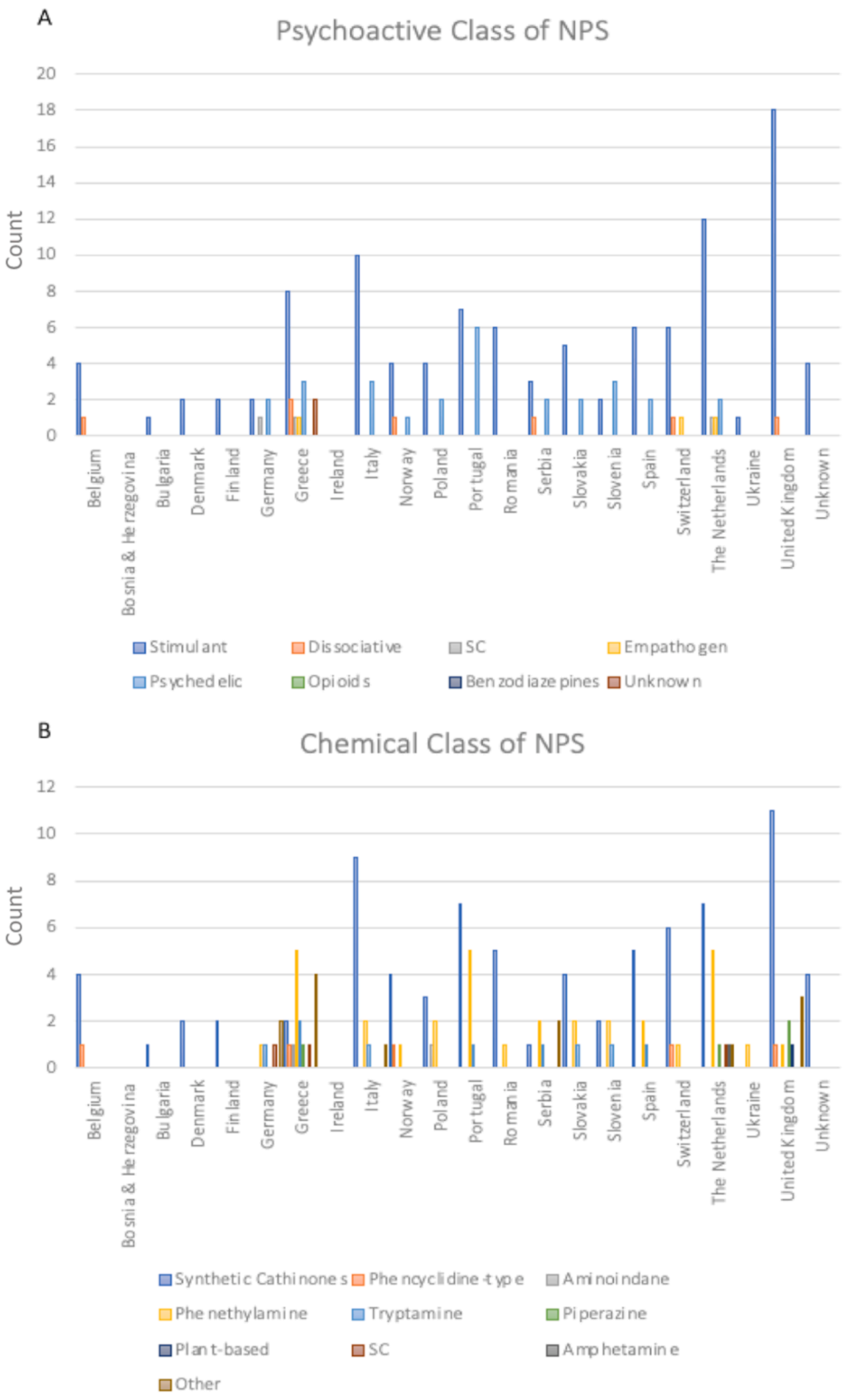

Fig. 3. Country-by-country breakdown of NPS frequency. A) Breakdown of psychoactive class of NPS found per country in reviewed articles. The United Kingdom detected the highest number of stimulant-type NPS out of all 21 countries. Portugal detected the highest number of psychedelic-type NPS out of all 21 countries. B) Breakdown of chemical class of NPS found per country in reviewed articles. The United Kingdom detected the highest number of synthetic cathinones out of all 21 countries. Greece, Portugal, and the Netherlands detected the highest number of phenethylamine-type NPS. Greece detected the largest variety of NPS chemical class.

identified psychoactive class of NPS were stimulants and psychedelics, while the most frequently identified chemical class were synthetic cathinones and phenethylamines. Geographically, most NPS were reported in Southern Europe which, along with Western Europe, recorded the largest variety of chemical and psychoactive classes. Studies focusing on Southern European countries have found a large variety of NPS also described in cross-sectional surveys (González et al., 2013; Korf et al., 2019) and police seizure data (Odoardi et al., 2016), corroborating the high number of NPS found in this review.

Previous case series and reports addressing clinical symptoms of acute toxicity associated with the use of synthetic cathinones highlight the presence of symptoms such as tachycardia, agitation, hypertension,

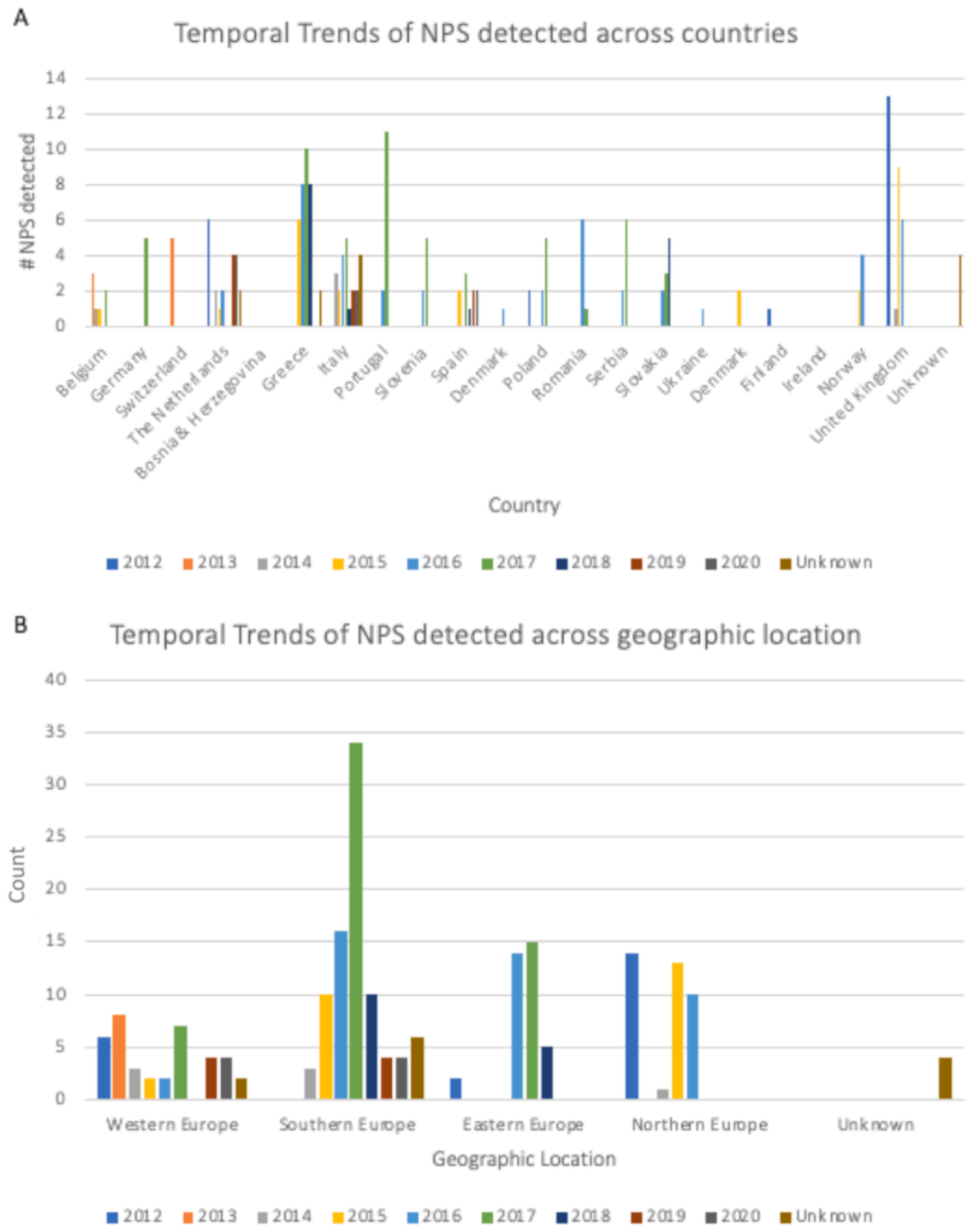

Fig. 4. Temporal trends of NPS. A) Temporal trends of NPS detected among countries, ranging from 2012 to 2020. Italy and Greece showed NPS detection across most years. B) Temporal trends of NPS detected across geographic locations, according to the United National Division of Statistics, with Southern Europe showing the greatest number of NPS, particularly in 2017. Western Europe showed NPS detection across every year except for 2018.

tremors, and hallucinations (Helander et al., 2013; Le Roux et al., 2015). Ingestion of NPS may not necessarily represent purported use or preference as products may be misleadingly sold to individuals as another illicit drug or NPS (European Monitoring Centre for Drugs and Drug Addiction 2021; Martins et al., 2017), further complicating the analysis of trends and related outcomes. Acute toxicity data from hospital admissions associated with NPS use show most cases involve polydrug combinations, where more than one substance has been ingested (Helander et al., 2020). As a result, NPS-users may experience a variety of adverse outcomes attributed poly-drug use (Van Hout et al., 2018), which in turn represent a challenge for clinical management and treatment. A small number of deaths were associated with the use of NPS (mostly mephedrone and synthetic cathinones), thus warning for their potential acute toxicity (Schifano et al., 2012; Zaami et al., 2018). Fatalities attributed to synthetic cathinones, based on postmortem toxicology reports, were associated with symptoms such as hyperthermia, hypertension, cardiac arrest, and evidence of serotonin syndrome (Zaami et al., 2018).

Mephedrone, a synthetic cathinone and stimulant, was the most prevalent NPS across all countries. Mephedrone's high levels across

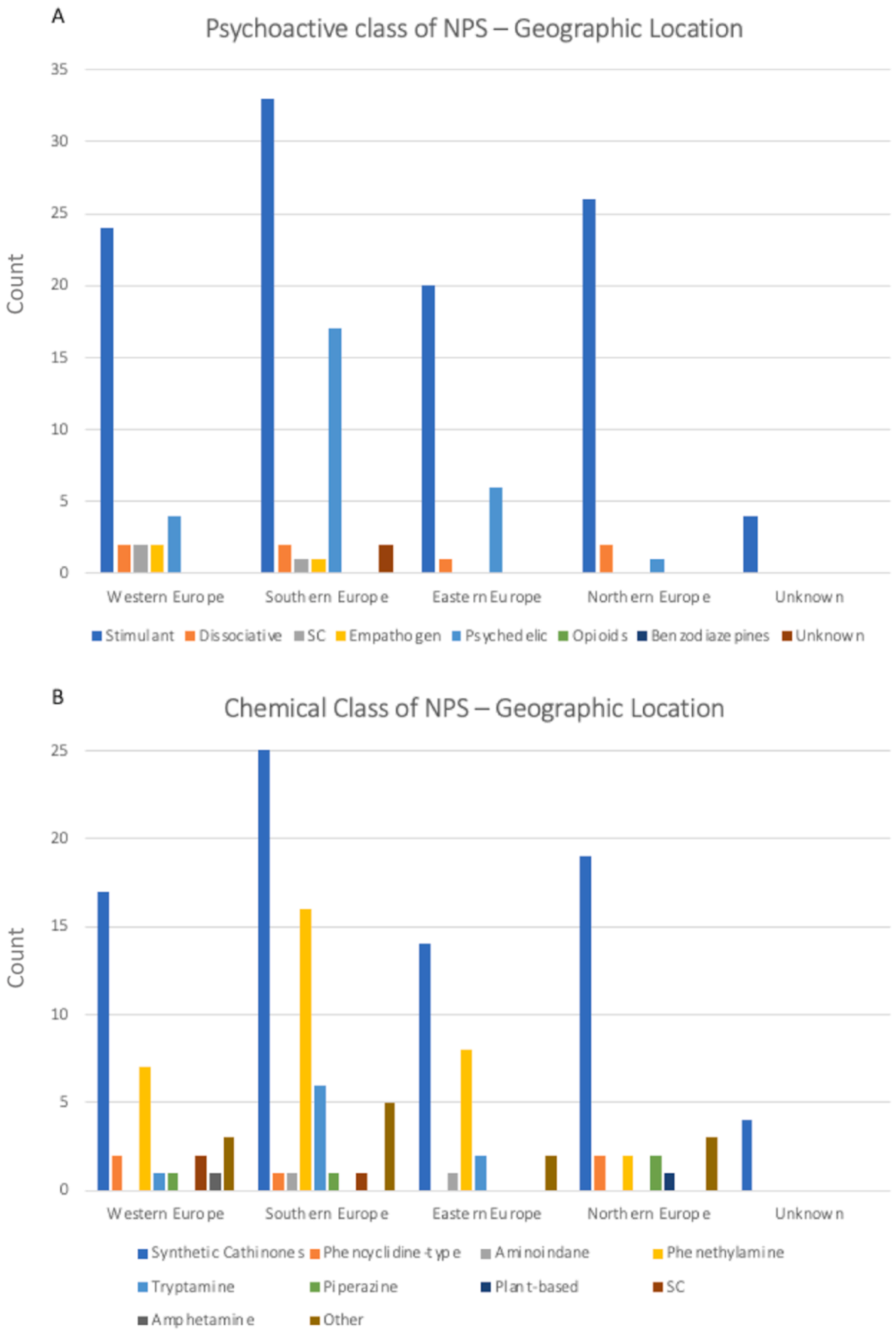

Fig. 5. Geographic NPS distribution by frequency described across studies. A) Breakdown of psychoactive class of NPS found per geographic region, based on the Statistical division of the United Nations, in reviewed articles. Southern Europe detected the highest number of NPS Compared to all other regions. Stimulant-type and psychedelic NPS were detected most in Southern Europe. Western Europe and Northern Europe detected the most phencyclidine-type NPS. Southern Europe and Western Europe showed the most variety among NPS. B) Breakdown of chemical class of NPS found per geographic region, based on the Statistical division of the United Nations. Southern Europe detected the greatest number of synthetic cathinones, phenethylamine-type NPS, and tryptamines. Western and Southern Europe detected the largest variety of chemical classes of NPS.

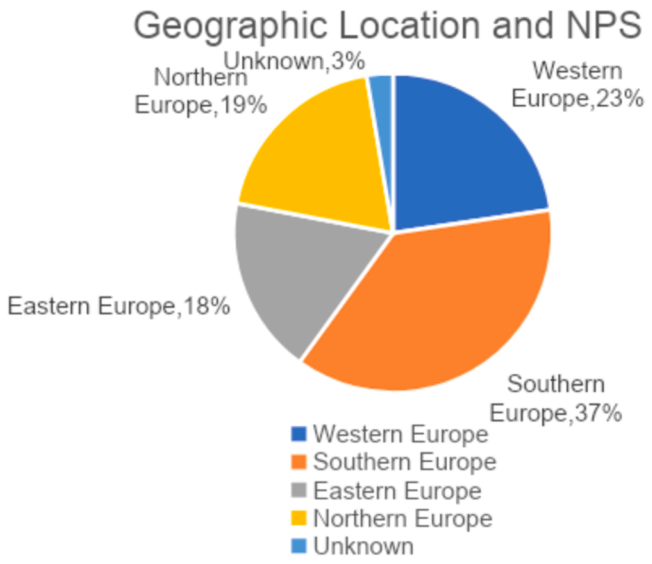

Fig. 6. Distribution of detected NPS across geographic location in Europe. Southern Europe detected the greatest number of NPS, compared to other regions.

countries is of particular interest. In 2009, the United Kingdom experienced an uptick in mephedrone use, with surveys indicating high lifetime prevalence above 40% among club-goers (Wood et al., 2012). High mephedrone use was also observed in a study conducted among psychonauts and festivalgoers in Spain, which showed a 35.2% prevalence among a sample of 230 participants (González et al., 2013). Lower mephedrone prevalence was found in Italy among nightclub recreational users, of whom 18.8% reported lifetime use of this substance (Vento et al., 2014).

While in the UK the enactment of the Psychoactive Substances Act of 2016 was followed by a decrease in acute toxicity presentations associated with synthetic cathinones (with no difference in the overall proportion of hospital presentations involving an NPS between 2015/2016 and 2016/2017) (Webb et al., 2019), a spike in hospital admissions associated with NPS has been observed in many European countries having implemented control measures over NPS (Neicun et al., 2022). However, toolkits and guidelines on clinical management, along with the establishment of the New Psychoactive Treatment UK Network have provided a means to educate professionals and provide adequate treatment (Abdulrahim and Bowden-Jones, 2015).

This review found temporal trends indicated a decrease in NPS presence in wastewater over time, potentially reflecting a decrease in NPS use. However, the EMCDDA describes a transition towards benzodiazepines-type NPS, new synthetic opioids (NSO), and SC (European Monitoring Centre for Drugs and Drug Addiction 2020; European Monitoring Centre for Drugs and Drug Addiction 2021), the former two not appearing across studies included in this review, and the latter detected at low frequency across three studies. Therefore, it is assumed that this may be due to the number of NPS tested in each study, NPS selected for study, and chosen countries varying across studies. Other detection methods indicate a higher prevalence of opioids, benzodiazepine, and SC use (Mensen et al., 2019, Di Trana et al., 2020, McNamara et al., 2019), with particular concern over adverse outcomes and fatalities (Batisse et al., 2020). Thus, it would be beneficial to further study these classes of NPS in WBE-epidemiology.

Interestingly, Hungary, a country with high NPS use among marginalized communities (Van Hout et al., 2018, Felvinczi et al., 2020), did not appear in any of the identified articles. Hard to reach populations such as marginalized communities may not be well-represented when recruiting participants from HRS, directly or indirectly. Analysis of drug paraphernalia may provide evidence of preference of NPS as a proxy, which has been used in previous studies (Gyarmathy et al., 2017) suggesting high synthetic cathinone preference. However, this does not consider users not seeking treatment currently, or those living in rural regions that do not have access to such services (Csák et al., 2020). Finally, no studies identified in this review included France, a country which has previously described NPS use, particularly associated with the misuse of medication (Batisse et al., 2020, Ponte et al., 2017). This may be due to the search strategy which excluded languages other than English.

Strengths and limitations

One of the limitations encountered in this study is the multiple outcome measurements used. Conversion from one unit to another was difficult without further descriptive information on flow rates, population or census size, or concentrations. Therefore, accurate prevalence rates could not be calculated. Furthermore, this study only focused on Europe while NPS use is nowadays a global phenomenon. Nevertheless, understanding European trends remains important for public health policymaking purposes.

Another limitation of this study is linked to the discrepancies in NPS definition. Over the years, the United Nations Office on Drugs and Crime (UNODC) has issued decisions on the legal status of multiple NPS, which no longer fall under the stated definition. Some studies were performed prior to the enactment of those decisions, thus some substances were classified as NPS at the time, including, but not limited to, Mephedrone and MXE. Other substances, including PMA, Pipradrol, and N-ethylamphetamine have been controlled under the Convention on Psychotropic Substances of 1971 since 1986, but were still treated as NPS in some studies. Therefore, findings from this study can provide insights into preference and trends in use to anticipate market responses, yet caution must be given to specificities pointed out in this review. Further information on UNODC decisions, scheduling dates, and sources can be found in Supplementary material (S7). We also were not able to assess drug instability or how they might react with sewage components, be adsorbed by the suspended solids, be biodegraded by the microbes in the sewage and biofilms, as well as self-hydrolysed. We were also not able to assess with this review the transformation processes during transport and storage of wastewater samples before analysis which one could assume that might change concentrations of different drugs to varying degrees. We also do not report on metabolites.

Finally, as NPS availability and demand are continually evolving, not all NPS were tested for each year, or across all countries, making it difficult to compare temporal and spatial trends across Europe. Moreover, as mostly largest cities were considered for WBE, findings from this study should be treated as preliminary evidence for preference and trends in use, yet they may not be considered as representative of all European countries. A limited number of studies do, however, consider population-wide analyses of a single country, and may provide a more in-depth assessment of patterns of NPS use. Although trends and preferences are in constant flux, and may not induce future outcomes, findings from this study cannot truly reflect current European-wide levels of use and preferences but do provide a snapshot of community-wide trends.

Furthermore, a major strength of WBE is the detection of NPS not previously identified in studies, thus providing better understanding of new NPS on the market, current trends in NPS use, and potential for further analysis in future WBE. Despite these limitations, this study provides relevant insights for a better NPS monitoring and public health policy design.

Conclusion

This is the first systematic review to synthesize wastewater-based epidemiology of NPS in Europe. Data found a preference towards synthetic cathinones and phenethylamines in chemical class. Also, trends in

Table 5
Quantifiable detection - ranges of NPS found in pooled urine- and wastewater-samples across 21 countries in Europe, given in concentration, ng/L and ug/L, and excreted mass loads, mg/day/1000 inhabitants.

Drug Name	Number of Countries	Geographic Location	Geographic Distribution	Concentration (ng/L)	Excreted mass load (mg/day/1000)	Concentration (ug/L)
2-PEA	1	Greece	SE	—	44.75	—
25iP-NBoMe	2	Serbia, Slovakia	EE, SE	—	0.14–0.60	—
3-MMC	3	Italy, Spain, The Netherlands	SE: 2 WE: 1	—	0.48 - 8.52	—
3,4-DMMC	2	Italy, Portugal	SE	—	0.10 - 0.20	—
4-FA	1	The Netherlands	WE	—	1.48	—
4-FMC	1	UK	NE	7.89		0.7
4-MEC	4	Italy, Poland, The Netherlands, UK	EE: 1 NE: 1 SE: 1 WE: 1	0.18 - 35.60	0.01	2.74
4,4′-DMAR	1	Serbia	SE	—	0.05	—
5-OH-DMT	1	Greece	SE	—	6.88	—
AB-CHIMINACA	1	Greece	SE	—	0.28	—
Alpha-PVP	2	Portugal, UK	NE, SE	—	0.17–3.31	9.18
Buphedrone	3	Italy, Portugal, Slovakia	EE: 1 SE: 2	0.74 - 3.38	0.20 - 1.77	—
Butylone	2	Romania, UK	EE, NE	—	0.53	0.3
Dipentylone	1	Unknown	Unknown	—	6.4	—
DMAA	1	Greece	SE	—	1.03	—
DMT	1	Greece	SE	—	1.3	—
Ethcathinone	1	Romania	EE	—	0.96	—
Ethylone	2	Spain, UK	NE, SE	11.57–20.69		—
Ethylphenidate	1	Greece	SE	—	0.73	—
MBZP	1	Greece	SE	—	0.67	—
MDAI	1	Greece	SE	—	2.55	—
MDPV	6	Finland, Italy, Norway, Switzerland, The Netherlands, UK	NE: 3 SE: 1 WE: 2	1.00 - 10.70	0.03 - 0.10	0.34
Mephedrone	10	Belgium, Denmark, Italy, Poland, Portugal, Romania, Slovakia, Slovenia, The Netherlands, UK	EE: 3 NE: 2 SE: 3 WE: 2	2.24 - 96.83	0.13 - 26.54	0.17 - 1.21
MePPP	1	Greece	SE	—	1.13	—
Methcathinone	10	Bulgaria, Italy, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Spain, The Netherlands	EE: 4 NE: 1 SE: 4 WE: 1	0.43 - 2.31	0.10 - 1.89	0.3
Methedrone	1	Greece	SE	—	0.83	—
Methoxyphenamine	1	Greece	SE	—	3.75	—
Methylone	6	Belgium, Denmark, Slovenia, Switzerland, Spain, The Netherlands	NE: 1 SE: 2 WE: 3	1.03 - 6.00	0.39 - 2.41	0.14 - 0.50
MXE	4	Belgium, Greece, Switzerland, UK	NE: 1 SE: 1 WE: 2	0.09 - 12.00	1.95	
N-Ethyl-Amphetamine	1	Greece	SE	—	0.6	
N, N-Dimethylcathinone	1	Spain	SE	0.7		
NEDPA	1	Serbia	SE	—	0.14	
Pentedrone	1	Slovakia	SE	1.80–8.61	0.50–2.80	
Pentylone	1	Romania	EE	—	0.35	
PMA	5	Greece, Romania, Serbia, Slovakia, The Netherlands	EE: 2 SE: 2 WE: 1	—	3.27 - 38.93	
PMMA	1	Greece	SE	—	12.4	

UK = United Kingdom; SE = Southern Europe; WE= Western Europe; NE = Northern Europe; EE = Eastern Europe; — = not provided.

NPS presence in wastewater indicated that preference towards stimulants and psychedelics varies across Europe. 2017 showed the highest number of NPS detected. Western and Southern Europe showed the highest number of NPS, compared to Northern and Eastern Europe. Quantifiable prevalence rates were difficult to establish due to the nature of data provided. Thus, this review has identified a need for a unified approach towards NPS-monitoring in WBE. Unified data obtained through the adoption of standard protocols would more accurately inform epidemiological surveillance and policy making. In turn, accurate comparable data will allow for targeted policymaking aimed at countering adverse outcomes and better anticipating future challenges, while considering specific trends and needs observed at national levels. Thus, a call for data-standardization is warranted in future WBE studies.

CRediT authorship contribution statement

Gabriel Gatica-Bahamonde: Formal analysis, Validation, Writing – original draft, Writing – review & editing, Visualization. **Elizabeth Alexandra Godynyuk:** Conceptualization, Methodology, Formal analysis, Validation, Investigation, Writing – original draft, Visualization. **Jessica Neicun:** Methodology, Formal analysis, Validation, Writing – original draft, Writing – review & editing, Visualization, Supervision. **Emmert Roberts:** Validation, Writing – review & editing. **Mehmet Mikail Tangerli:** Methodology, Investigation, Formal analysis. **Robin van Kessel:** Validation, Writing – review & editing. **Katarzyna Czabanowska:** Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing, Supervision. **Keith Humphreys:** Validation, Writing – review & editing. **Andres Roman-Urrestarazu:** Conceptualization, Methodology, Formal analysis, Validation, Writing – original draft, Writing – review & editing, Visualization, Supervision.

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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.etdah.2023.100053.

References

Abdulrahim, D, Bowden-Jones, O, 2015. Group obotNE. Guidance on the Management of Acute and Chronic Harms of Club Drugs and New Psychoactive Substances. New Psychoactive Treatment UK Network (NEPTUNE), London.

Archer, JR, Dargan, PI, Lee, HM, Hudson, S, Wood, DM., 2014. Trend analysis of anonymised pooled urine from portable street urinals in central London identifies variation in the use of New psychoactive substances. Clin. Toxicol. (Phila) 52 (3), 160–165.

Bade, R, Bijlsma, L, Sancho, JV, Baz-Lomba, JA, Castiglioni, S, Castrignanò, E, et al., 2017. Liquid chromatography-tandem mass spectrometry determination of synthetic cathinones and phenethylamines in influent wastewater of eight European cities. Chemosphere 168, 1032–1041.

Bade, R, White, JM, Chen, J, Gerber, C, Baz-Lomba, JA, Been, F, et al., 2021. International snapshot of new psychoactive substance use: case study of eight countries over the 2019/2020 new year period. Water Res. 193, 116891.

Batisse, A, Eiden, C, Peyriere, H, Djezzar, S., 2020. Use of new psychoactive substances to mimic prescription drugs: the trend in France. Neurotoxicology 79, 20–24.

Bijlsma, L, Celma, A, Castiglioni, S, Salgueiro-González, N, Bou-Iserte, L, Baz-Lomba, JA, et al., 2020. Monitoring psychoactive substance use at six European festivals through wastewater and pooled urine analysis. Sci. Total Environ. 725, 138376.

Bijlsma, L, Picó, Y, Andreu, V, Celma, A, Estévez-Danta, A, González-Mariño, I, et al., 2021. The embodiment of wastewater data for the estimation of illicit drug consumption in Spain. Sci. Total Environ. 772, 144794.

Brandeburová, P, Bodík, I, Horáková, I, Žabka, D, Castiglioni, S, Salgueiro-González, N, et al., 2020. Wastewater-based epidemiology to assess the occurrence of new psychoactive substances and alcohol consumption in Slovakia. Ecotoxicol. Environ. Saf. 200, 110762.

Castiglioni, S, Salgueiro-González, N, Bijlsma, L, Celma, A, Gracia-Lor, E, Beldean-Galea, MS, et al., 2021. New psychoactive substances in several European populations assessed by wastewater-based epidemiology. Water Res. 195, 116983.

Catalani, V, Arillotta, D, Corkery, JM, Guirguis, A, Vento, A, Schifano, F., 2021. Identifying new/emerging psychoactive substances at the time of COVID-19; a web-based approach. Front. Psychiatry 11.

Catalani, V, Townshend, HD, Prilutskaya, M, Roman-Urrestarazu, A, van Kessel, R, Chilcott, RP, Banayoti, H, McSweeney, T, Corazza, O, 2023. Profiling the vendors of COVID-19 related product on the Darknet: an observational study. Emerg. Trends Drugs Addict. Health. 3, 100051. https://doi.org/10.1016/j.etdah.2023.

Causanilles, A, Kinyua, J, Ruttkies, C, van Nuijs, ALN, Emke, E, Covaci, A, et al., 2017. Qualitative screening for new psychoactive substances in wastewater collected during a city festival using liquid chromatography coupled to high-resolution mass spectrometry. Chemosphere 184, 1186–1193.

Celma, A, Sancho, JV, Salgueiro-González, N, Castiglioni, S, Zuccato, E, Hernández, F, et al., 2019. Simultaneous determination of new psychoactive substances and illicit drugs in sewage: potential of micro-liquid chromatography tandem mass spectrometry in wastewater-based epidemiology. J. Chromatogr. A 1602, 300–309.

Corkery, JM, Schifano, F, Martinotti, G., 2020. How deaths can help clinicians and policy-makers understand the risks of new psychoactive substances. Br. J. Clin. Pharmacol. 86 (3), 482–498.

Csák, R, Szécsi, J, Kassai, S, Márványkövi, F, Rácz, J., 2020. New psychoactive substance use as a survival strategy in rural marginalised communities in Hungary. Int. J. Drug Policy 85, 102639.

Diamanti, K, Aalizadeh, R, Alygizakis, N, Galani, A, Mardal, M, Thomaidis, NS., 2019. Wide-scope target and suspect screening methodologies to investigate the occurrence of new psychoactive substances in influent wastewater from Athens. Sci. Total Environ. 685, 1058–1065.

Di Trana, A, Pirani, F, La Maida, N, Busardo, FP, Mannocchi, G, Gottardi, M, et al., 2020. A comprehensive HPLC-MS-MS screening method for 77 new psychoactive substances, 24 classic drugs and 18 related metabolites in blood, urine, and oral fluid. J. Anal. Toxicol. 44 (8), 769–783.

Escolà Casas, M, Schröter, NS, Zammit, I, Castaño-Trias, M, Rodriguez-Mozaz, S, Gago-Ferrero, P, et al., 2021. Showcasing the potential of wastewater-based epidemiology to track pharmaceuticals consumption in cities: comparison against prescription data collected at fine spatial resolution. Environ. Int. 150, 106404.

European Monitoring Centre for Drugs and Drug Addiction, 2020. New Psychoactive substances: Global markets, Glocal Threats and the COVID-19 pandemic. An update from the EU Early Warning System (December 2020). Luxembourg: Publications Office of the European Union.

European Monitoring Centre for Drugs and Drug Addiction, 2021b. New Benzodiazepines in Europe - a review. Publications Office of the European Union, Luxembourg.

European Monitoring Centre for Drugs and Drug Addiction, 2021a. European Drug Report 2021: Trends and Developments. Luxembourg: Publications Office of the European Union.

European Parliament and Council of the European Union. Commission Staff Working Document Impact Assessment Accompanying the Document Proposal For A Regulation of the European Parliament And Of The Council On New Psychoactive Substances And Proposal For A Directive Of The European Parliament And Of The Council Amending Council Framework Decision 2004/757/Jha Of 25 October 2004 Laying Down Minimum Provisions On The Constituent Elements Of Criminal Acts And Penalties In The Field Of Illicit Drug Trafficking, As Regards The Definition Of Drug 2013 [Available from: https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX:52013SC0319].

Felvinczi, K, Benschop, A, Urbán, R, Van Hout, MC, Dąbrowska, K, Hearne, E, et al., 2020. Discriminative characteristics of marginalised new psychoactive users: a transnational study. Int. J. Ment. Health Addict. 18 (4), 1128–1147.

Feng, L, Zhang, W, Li, X., 2018. Monitoring of regional drug abuse through wastewater-based epidemiology—a critical review. Sci. China Earth Sci. 61 (3), 239–255.

Gent, L, Paul, R., 2021. The detection of new psychoactive substances in wastewater. A comprehensive review of analytical approaches and global trends. Sci. Total Environ. 776.

Giese, C, Igoe, D, Gibbons, Z, Hurley, C, Stokes, S, McNamara, S, et al., 2015. Injection of new psychoactive substance snow blow associated with recently acquired HIV infections among homeless people who inject drugs in Dublin, Ireland, 2015. Eurosurveillance 20 (40).

González, D, Ventura, M, Caudevilla, F, Torrens, M, Farre, M., 2013. Consumption of new psychoactive substances in a Spanish sample of research chemical users. Hum. Psychopharmacol. 28 (4), 332–340.

González-Mariño, I, Baz-Lomba, JA, Alygizakis, NA, Andrés-Costa, MJ, Bade, R, Bannwarth, A, et al., 2020. Spatio-temporal assessment of illicit drug use at large scale: evidence from 7 years of international wastewater monitoring. Addiction 115 (1), 109–120. Jan 1.

González-Mariño, I, Gracia-Lor, E, Bagnati, R, Martins, CP, Zuccato, E, Castiglioni, S., 2016a. Screening new psychoactive substances in urban wastewater using high resolution mass spectrometry. Anal. Bioanal. Chem. 408 (16), 4297–4309.

González-Mariño, I, Gracia-Lor, E, Rousis, NI, Castrignanò, E, Thomas, KV, Quintana, JB, et al., 2016b. Wastewater-based epidemiology to monitor synthetic cathinones use in different European countries. Environ. Sci. Technol. 50 (18), 10089–10096.

Graziano, S, Anzillotti, L, Mannocchi, G, Pichini, S, Busardò, FP., 2019. Screening methods for rapid determination of new psychoactive substances (NPS) in conventional and non-conventional biological matrices. J. Pharm. Biomed. Anal. 163, 170–179.

Gyarmathy, VA, Péterfi, A, Figeczki, T, Kiss, J, Medgyesi-Frank, K, Posta, J, et al., 2017. Diverted medications and new psychoactive substances-A chemical network analysis of discarded injecting paraphernalia in Hungary. Int. J. Drug Policy 46, 61–65.

Helander, A, Bäckberg, M, Beck, O., 2020. Drug trends and harm related to new psychoactive substances (NPS) in Sweden from 2010 to 2016: experiences from the STRIDA project. PLoS One 15 (4), e0232038.

Helander, A, Beck, O, Hägerkvist, R, Hultén, P., 2013. Identification of new psychoactive drug use in Sweden based on laboratory analysis – initial experiences from the STRIDA project. Scand. J. Clin. Lab. Invest. 73 (5), 400–406.

Hoy, D, Brooks, P, Woolf, A, Blyth, F, March, L, Bain, C, et al., 2012. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J. Clin. Epidemiol. 65 (9), 934–939.

Iwersen-Bergmann, S, Lehmann, S, Heinemann, A, Schröder, C, Müller, A, Jungen, H, et al., 2019. Mass poisoning with NPS: 2C-E and Bromo-dragon fly. Int. J. Legal Med. 133 (1), 123–129.

Kankaanpää, A, Ariniemi, K, Heinonen, M, Kuoppasalmi, K, Gunnar, T., 2014. Use of illicit stimulant drugs in Finland: a wastewater study in ten major cities. Sci. Total Environ. 487, 696–702.

Khaled, SM, Hughes, E, Bressington, D, Zolezzi, M, Radwan, A, Badnapurkar, A, et al., 2016. The prevalence of new psychoactive substances (NPS) use in non-clinical populations: a systematic review protocol. Syst. Rev. 5 (1).

Kinyua, J, Covaci, A, Maho, W, McCall, AK, Neels, H, van Nuijs, AL., 2015. Sewage-based epidemiology in monitoring the use of new psychoactive substances: validation and application of an analytical method using LC-MS/MS. Drug Test. Anal. 7 (9), 812–818.

Korf, D, Benschop, A, Werse, B, Kamphausen, G, Felvinczi, K, Dabrowska, K, et al., 2019. How and where to find NPS users: a comparison of methods in a cross-national survey among three groups of current users of new psychoactive substances in Europe. Int. J. Ment. Health Addict.

Larabi, IA, Mayer, C, Anderson, V, Etting, I, Cahir, D, Fabresse, N, et al., 2019. Rapid screening of NPS and conventional drugs of abuse (DoA) using a biochip array technology (BAT) in whole blood and urine samples from forensic and clinical cases: a comparative study. Toxicologie Analytique et Clinique 31, S63–SS4, 2, Supplement.

Le Roux, G, Bruneau, C, Lelièvre, B, Deguigne, MB, Turcant, A, Harry, P, et al., 2015. Recreational phenethylamine poisonings reported to a French poison control center. Drug Alcohol Depend. 154, 46–53.

Martins, D, Barratt, MJ, Pires, CV, Carvalho, H, Vilamala, MV, Espinosa, IF, et al., 2017. The detection and prevention of unintentional consumption of DOx and 25x-NBOMe at Portugal's boom festival. Hum. Psychopharmacol. 32 (3).

McAuley, A, Yeung, A, Taylor, A, Hutchinson, SJ, Goldberg, DJ, Munro, A., 2019. Emergence of new psychoactive substance injecting associated with rapid rise in the population prevalence of hepatitis C virus. Int. J. Drug Policy 66, 30–37.

McNamara, S, Stokes, S, Nolan, J., 2019. The emergence of new psychoactive substance (NPS) benzodiazepines. A survey of their prevalence in opioid substitution patients using LC-MS. Ir. Med. J. 112 (7).

Mensen, VT, Vreeker, A, Nordgren, J, Atkinson, A, De La Torre, R, Farré, M, et al., 2019. Psychopathological symptoms associated with synthetic cannabinoid use: a comparison with natural cannabis. Psychopharmacology (Berl.) 236 (9), 2677–2685.

Moritz, E., Austin, C., Wahl, M., DesLauriers, C, Navon, L, Walblay, K, et al., 2018. Notes from the field: outbreak of severe illness linked to the vitamin k antagonist Brodifacoum and use of synthetic cannabinoids — Illinois. March–April 2018 MMWR Morb. Mortal. Wkly. Rep. 67 (21), 607–608.

Neicun, J, Roman-Urrestarazu, A, Czabanowska, K., 2022. Legal responses to New psychoactive substances implemented by ten European countries: an analysis from legal epidemiology. Emerging Trends in Drugs, Addict. Health 2, 100044.
Odoardi, S, Romolo, FS, Strano-Rossi, S., 2016. A snapshot on NPS in Italy: distribution of drugs in seized materials analysed in an Italian forensic laboratory in the period 2013-2015. Forensic Sci. Int. 265, 116–120.
Page, MJ, McKenzie, JE, Bossuyt, PM, Boutron, I, Hoffmann, TC, Mulrow, CD, et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst. Rev. 10 (1), 89.
Pirona, A, Bo, A, Hedrich, D, Ferri, M, Van Gelder, N, Giraudon, I, et al., 2017. New psychoactive substances: current health-related practices and challenges in responding to use and harms in Europe. Int. J. Drug Policy 40, 84–92.
Ponte, C, Jouanjus, E, Lapeyre-Mestre, M, Pi, C, Palmaro, A., 2017. Early signal of diverted use of tropicamide eye drops in France. Br. J. Clin. Pharmacol. 83 (8), 1791–1800.
Reuter, P, Caulkins, JP, Midgette, G., 2021. Heroin use cannot be measured adequately with a general population survey. Addiction.
Rice, J, Kannan, AM, Castrignanò, E, Jagadeesan, K, 2020. Kasprzyk-Hordern B. Wastewater-based epidemiology combined with local prescription analysis as a tool for temporalmonitoring of drugs trends - A UK perspective. Sci. Total Environ. 735, 139433.
Richeval, C, Wille, SMR, Nachon-Phanithavong, M, Samyn, N, Allorge, D, Gaulier, JM., 2018. New psychoactive substances in oral fluid of French and Belgian drivers in 2016. Int. J. Drug Policy 57, 1–3.
Salgueiro-González, N, Castiglioni, S, Gracia-Lor, E, Bijlsma, L, Celma, A, Bagnati, R, et al., 2019. Flexible high resolution-mass spectrometry approach for screening new psychoactive substances in urban wastewater. Sci. Total Environ. 689, 679–690.
Savulich, G, Bowden-Jones, O, Stephenson, R, Brühl, AB, Ersche, KD, Robbins, TW, et al., 2021. Hot" and "Cold" cognition in users of club drugs/new psychoactive substances. Front. Psychiatry 12 (333).
Schifano, F, Corkery, J, Ghodse, AH., 2012. Suspected and confirmed fatalities associated with mephedrone (4-methylmethcathinone, "meow meow") in the United Kingdom. J. Clin. Psychopharmacol. 32 (5), 710–714.
Shafi, A, Gallagher, P, Stewart, N, Martinotti, G, Corazza, O., 2017. The risk of violence associated with new psychoactive substance misuse in patients presenting to acute mental health services. Human Psychopharmacol. 32 (3), e2606.
Soussan, C, Andersson, M, Kjellgren, A, 2018. The diverse reasons for using new psychoactive substances - a qualitative study of the users' own perspectives. Int. J. Drug Policy 52, 71–78.
Stephenson G RA. New Psychoactive Substances in England: a review of the evidence 2014 [Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/368587/NPSevidenceReview.pdf].
Styszko, K, Dudarska, A, Zuba, D., 2016. The presence of stimulant drugs in wastewater from Krakow (Poland): a snapshot. Bull. Environ. Contam. Toxicol. 97 (3), 310–315.
Sulej-Suchomska, AM, Klupczynska, A, Dereziński, P, Matysiak, J, Przybyłowski, P, Kokot, ZJ., 2020. Urban wastewater analysis as an effective tool for monitoring illegal drugs, including new psychoactive substances, in the Eastern European region. Sci. Rep. 10 (1), 4885.
Sutherland, R, Bruno, R, Peacock, A, Dietze, P, Breen, C, Burns, L, et al., 2017. New psychoactive substances: purchasing and supply patterns in Australia. Human Psychopharmacol. 32 (3), e2577.
Thomas, K.v., Bijlsma, L, Castiglioni, S, Covaci, A, Emke, E, Grabic, R, et al., 2012. Comparing illicit drug use in 19 European cities through sewage analysis. Sci. Total Environ. 432, 432–439. Aug 15.
United Nations Office on Drugs and Crime, 2013. World Drug Report 2013. United Nations, Vienna.
Van Hout, MC, Benschop, A, Bujalski, M, Dąbrowska, K, Demetrovics, Z, Felvinczi, K, et al., 2018. Health and social problems associated with recent new psychoactive substance (NPS) use amongst marginalised, nightlife and online users in six European countries. Int. J. Ment. Health Addict. 16 (2), 480–495.
Vento, AE, Martinotti, G, Cinosi, E, Lupi, M, Acciavatti, T, Carrus, D, et al., 2014. Substance use in the club scene of Rome: a pilot study. Biomed. Res. Int. 2014, 617546.
Webb, NE, Wood, DM, Greene, SL, Hunter, LJ, Archer, JRH, Dines, AM, et al., 2019. Change in the new psychoactive substances associated with emergency department acute toxicity presentations associated with the introduction of the UK 2016 psychoactive substances act. Clin. Toxicol. (Phila) 57 (1), 36–41.
Werse, B, Benschop, A, Kamphausen, G, Van Hout, M-C, Henriques, S, Silva, JP, et al., 2019. Sharing, group-buying, social supply, offline and online dealers: how users in a sample from six European countries procure new psychoactive substances (NPS). Int. J. Ment. Health Addict. 17 (5), 1237–1251.
Wood, DM, Hunter, L, Measham, F, Dargan, PI., 2012. Limited use of New psychoactive substances in South London nightclubs. QJM 105 (10), 959–964.
Zaami, S, Giorgetti, R, Pichini, S, Pantano, F, Marinelli, E, BusardÚ, F, 2018. Synthetic cathinones related fatalities: an update. Eur. Rev. Med. Pharmacol. Sci. 22 (1), 268–274.
Zawilska, JB, Andrzejczak, D., 2015. Next generation of New psychoactive substances on the horizon – A complex problem to face. Drug Alcohol Depend. 157, 1–17.
Zuccato, E, Chiabrando, C, Castiglioni, S, Bagnati, R, Fanelli, R., 2008. Estimating community drug abuse by wastewater analysis. Environ. Health Perspect. 116 (8), 1027–1032.