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Online test purchased new psychoactive substances in 5 different European countries; a snapshot study of chemical composition and price

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Abstract: Background: New psychoactive substances (NPS) are on offer worldwide online, in order to shed light on the purity and price of these substances in the European Union, a research collaboration was set up involving France, United Kingdom (UK), the Netherlands, Czech Republic and Poland.
Methods: Per country, around 10 different NPS were test purchased from different webshops. Then, chemical analysis of NPS was done with according reference standards to identify and quantify the contents.
Results: In contrast to what is generally advertised on the webshops (>99%), purity varied considerably per test purchased NPS. Several NPS were mislabelled, some containing chemical analogues (e.g. 25B/C-NBOMe instead of 25I-NBOMe, pentedrone instead of 3,4-DMMC). But in some cases NPS differed substantially from what was advertised (e.g. pentedrone instead of AMT or 3-FMC instead of 5-MeO-DALT). Per gram, purity-adjusted prices of cathinones differed substantially between three countries of test purchase, with Poland being the least expensive. Synthetic cannabinoids were relatively the most expensive in the Czech Republic and least expensive in the UK.
Conclusions: The current findings provides a snapshot of the price and chemical contents of NPS products purchased by different countries and in different webshops. There is a potential danger of mislabelling of NPS. The great variety in price and purity of the delivered products might be the result of the market dynamics of supply and demand and the role of law enforcement in different European countries.

Online test purchased new psychoactive substances in 5 different European countries; a snapshot study of chemical composition and price

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Introduction

In recent years, the worldwide illicit drug market is characterized by a continuous emergence of the marketing and sale of newly designed psychoactive substances mimicking the effects of internationally controlled substances (such as cocaine, ecstasy or amphetamine). These new psychoactive substances (NPS) arise from entrepreneurial endeavours where ideas for their creation are inspired by patents, scientific literature, existing controlled drugs of abuse and medicines known to have psychoactive properties (Brandt, King, & Evans-Brown, 2014). For instance, some NPS follow similar molecular scaffolds as their illicit counterparts but might slightly differ in chemical composition of the molecule (Saha et al., 2015; Simmler et al., 2013). These alterations can impact greatly on the specific activities of a compound. For instance, neurotransmitter transporter affinity could be significantly altered, resulting in substances that block serotonin or dopamine reuptake more effectively (Baumann et al., 2014; Marusich et al., 2014; Saha et al., 2015). Whereas many of these alterations were designed to circumvent law enforcement, they could have a grave impact on the health of the drug user, like an increased risk of overdosing.

Increasing awareness about harms associated with NPS use also requires a multi-disciplinary and targeted approach (European Monitoring Centre for Drugs and Drug Addiction, 2016a). The diversity of substances has increased dramatically in the last few years. This is reflected in the number (> 560) and nature of substances currently monitored by the European Union's Early Warning System that is coordinated by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Among a range of other substances, types of compounds frequently recorded include cathinones, opioids, benzodiazepines or synthetic cannabinoids (a chemically highly diverse groups of compounds) (EMCDDA Europol, 2016).

The sale of these substances is mostly facilitated through freely accessible Internet shops (webshops). In 2013, the EMCDDA conducted a snapshot study which revealed 651 different webshops offering a variety of NPS globally (European Monitoring Centre for Drugs and Drug Addiction, 2016b). Some of these substances are also being sold by vendors through the dark web, an Internet space not accessible with standard search engines (Barratt et al., 2016). Recent research identified 1031 different vendors on the dark web selling substances and 10,927 individual drug listings (Aldridge et al., 2016). However, vendors on the dark web also offer many other substances too, including illicit substances, and most of the 10,927 drug listings fell into either of six categories: psychedelics, stimulants, opioids, cannabis, ecstasy and prescription drugs. NPS were mainly found under psychedelics or stimulants.

From a health policy and clinical perspective, there is great concern surrounding the rapid emergence of NPS, their lack of regulation, open sale and a lack of evidence on their effects and harms (Coulson & Caulkins, 2012; European Monitoring Centre for Drugs and Drug Addiction, 2015; Seddon et al., 2014; UNODC, 2013; van Amsterdam, Nutt, & van den Brink, 2013). Besides this, there is the risk of mislabelling with NPS available through freely accessible websites which are virtually uncontrolled and unlimited. Well-known examples of false and misleading labelling is by giving these drugs meaningless and generic brand names, like "spice" or "K2" (Baumann et al., 2014; Baumann, Partilla, & Lehner, 2013; Seely et al., 2013; Spaderna, Addy, & D'Souza, 2013). However, mislabelling by selling one compound as another also occurs and can be equally or more dangerous. Several recent cases have been noted where very potent compounds were sold as less potent analogues, increasing the risk of dosage-related adverse effects (Gee, Schep, Jensen, Moore, & Barrington, 2016; Walterscheid et al., 2014).

As a result, stakeholders associated with healthcare, forensics and policy-making are continuously faced with the challenge of collecting evidence for risk assessments of these unknown substances (Zamengo, Frison, Bettin, & Sciarrone, 2014). Another issue that has been raised in recent years is the difficulty in the identification of NPS in seized samples or biological specimens, as their variation is ever-increasing and routine toxicological laboratory screenings are not always up to the challenge of keeping track of the rapid emergence of these new substances or their metabolites (Favretto, Pascali, & Tagliaro, 2013). Standard immunoassay methodology often does not discriminate between all these molecular variants of chemical classes of NPS. In addition, absence of appropriate reference material and scarce analytical information about newly encountered NPS adds challenges even in the presence of state-of-the-art instrumentation. Furthermore, such systems may be out of reach for laboratories that are situated in economically less privileged countries, meaning that many NPS go undetected and are not reported to early warning systems operating worldwide (UNODC, 2013).

The availability of substances, popularity, prevalence of use and distribution of NPS, however, is not necessarily identical in each country and reasons for this might include cultural differences, geographical location and different legislation (UNODC, 2016). In order to shed light on the diverse nature of NPS distribution and newly emerging drugs that are being offered through online shops across European countries, an international research collaboration was supported by the European Commission to investigate the online NPS market. Entitled the Internet Tools for Research in Europe on New Drugs (I-TREND, www.i-trend.eu), the project involved five collaborating institutions in different countries:

Observatoire français des drogues et des toxicomanies (OFDT) in France, Liverpool John Moores University (LJMU) in the United Kingdom (UK), the Netherlands Institute of Mental Health and Addiction (Trimbos institute) in the Netherlands, the Charles University in Prague (CUNI) of the Czech Republic and the SWPS University of Social Sciences and Humanities (SWPS) in Poland. This collaborative endeavour was undertaken between 2014-2015 and collected a variety of data on NPS, such as availably and marketing of NPS via online European webshops and the chemical analysis of NPS that were purchased online (for more details of the general scheme, see http://www.emcdda.europa.eu/system/files/publications/2155/TDXD16001ENN_FINAL.pdf) . In the present study, the chemical analysis part of the project is described to identify the contents of the ten most relevant NPS purchased per country. This is followed by an analysis of average purity, price and adulteration of the test purchased NPS products and identification of potential mismatch between contents and the product advertised (mislabelling).

Methods

Selection of NPS and webshops

Each partner country selected about ten NPS (aka the Top List) on the basis of available information sources. Firstly, data from the national Reitox European Union Early Warning System (EU EWS) were consulted. It reports on police seizures, fatal and non-fatal intoxication data, as well as forensic and toxicological data when available. Secondary, when the EWS data was not considered useful or retrieved too little information, extensive data were collected from national poisoning information centres (e.g. National Poisons Information Service, UK), national (e.g. British Crime Survey in the UK), international drugs surveys (the Global Drug Survey), drug user forums and drug sampling data from nationally imbedded drug testing systems (e.g. DIMS in the Netherlands or SINTES in France) (Giraudon and Bello, 2009; Niesink and Brunt, 2011; Global Drug Survey, 2016; Office for National Statistics, 2016).

Then, webshops were selected for ordering the NPS. Server location and IP address were not the most reliable criteria for the selection of webshops for the different partner countries, as various webshops hold servers abroad and due to the nature of the online market, which is unbound and not restricted by the same rules that apply to the domestic wholesale market. Therefore, the criteria for webshop selection were the language in which the webshop presented itself, advertised its products and its shipment constrictions, which indicated at

which consumer market it was predominantly targeted. Also, only webshops that were accessible on the surface web were selected, cryptomarkets on the dark web were excluded. Another selection criterion was that the webshops would sell and promote one of the NPS selected, this confined the search to a proportion of available webshops. The largest and highest google-indexed webshops were chosen on the basis of this. In order to avoid legal problems with purchasing substances, it was decided to preferably order NPS not controlled at the time of purchase.

In some instances, webshops were selling and promoting newly synthesized compounds as replacements for substances just put under control (for instance, when a substance had been implicated in a fatal intoxication). Whether such substances often emerged too recent to be found in seizure data, they were included in a national NPS Top List anyway to acknowledge this issue. For example, both 5- and 6-APB were initially included in the UK Top List based on seizure data. However, due to their rapid inclusion into legislative control (The Stationery Office, 2013), availability and advertisement on UK-based webshops decimated. Between the announcement of the 5/6-APB ban and its definitive confirmation, the 'follow-up' substance 5-EAPB was highly being discussed about on British forums as 5/6-APB replacement and also being sold and promoted on UK webshops and this NPS was thus included in the UK Top List of test purchases instead. Notably, synthetic cannabinoids were not selected by the Netherlands in this study, since there was an absence of webshops marketing these substances in the Netherlands and the virtual absence of synthetic cannabinoids in the Dutch EWS and DIMS data.

Test purchases

Each I-TREND partner separately purchased NPS from webshops using a variety of payment methods, such as prepaid credit card, credit cards or bank wire transfer (e.g. through PayPal™). It was also aimed to avoid traceability to the institutions in order to maintain appearance as individual customers. The Top List contained test purchases of around 10 NPS per country and it was strived to test purchase these at 4 different webshops, resulting in 40 NPS test purchases per partner institute. In the case of non-reception of the parcel there was no further follow-up or contact with the supplier.

The Trimbos institute in the Netherlands formed an exception to this purchasing process, since it has its continuous flow of NPS drug samples through the Drug Information and Monitoring System (DIMS) and it was expected that all NPS of the Top List would be

handed in during the two-year period of sample collection. For a description of the DIMS, see (Niesink and Brunt, 2011). At the DIMS, specifically for the I-TREND project, the drug consumers were asked additional questions, such as source of purchase on the Internet (webshops) and price. Samples without this information, or samples not purchased from the Internet, were excluded from the study.

Laboratory analysis

Reference standards (50 mg) for the different NPS were obtained from LGC standards™ (LGC Standards, Middlesex, Teddington, UK). Both qualitative and quantitative examinations of the received NPS were employed using standard methods of analysis, such as gas chromatography and liquid chromatography (LC) coupled to mass spectrometry (MS) and LC and GC combined with diode array detection (DAD) or flame ionization detector (FID). Shortly, CUNI, SWPS, DIMS, LJMU and OFDT used LC-MS, LC-MS/MS, LC-DAD, GC-MS and GC-FID. For some compounds, OFDT, CUNI and SWPS also used GC and Quadrupole Time-of-Flight (QTOF) methodology and GC-MS/MS for better identification and quantification. Basically, most quantitative methods overlapped between all laboratories and this wasn't expected to have a major impact on the results (see Table S5 for overview of laboratory techniques).

Price analysis

Prices of the different NPS purchased from webshops were compared. British Pound Sterling (GBP), Czech Koruna (CZK) and Polish Zloty were converted to Euro, based on the average currency exchange rate between June 2014 and February 2015, the time during which the online test purchases were conducted. Average prices of NPS per gram per country, average price per NPS and average price overall were calculated. In addition, purity adjusted prices were also calculated per individual NPS, consistent with procedures reported in the scientific literature about drug market dynamics (Caulkins et al., 2007). In addition, prices were converted into purchasing power parities (PPPs), an economic measure that's designed to compare prices between different countries. PPPs serve as a way to take gross domestic product and inflation into account for a certain country based on goods that are highly comparable. For this study, NPS prices were adjusted with Eurostat-published PPP for alcohol, tobacco and narcotics, in order to estimate the relative price of NPS in comparison with their nearest substitute goods (Eurostat-OECD, 2012). Standard deviations (± S.D.) are given.

Results

The number of webshops selected for test purchase varied per country: The Netherlands (20), United Kingdom (5), France (11), Czech Republic (6), Poland (5). Most webshops had IP addresses that indicated that they originated from the countries of test purchase, except for France, which had no webshops originating from that country. Instead, all their purchases came from webshops located in the UK, but their IP address was different from those of the webshops which the UK selected. Moreover, there were no overlapping webshops between countries based on IP address. Most webshops advertised their NPS products as >90% pure or higher. In total, 200 NPS products were test purchased by the 5 partner countries under 31 different chemical NPS names. Chemical names, abbreviations, chemical class and main effect of these 31 NPS are given in Table 1. Eighteen orders were never delivered and one analysis had not been performed by the laboratory. Consequently, 182 analyses were conducted and 34 different compounds identified. 15 NPS were obtained by more than one partner country, whereas 16 NPS were unique to a specific country (Table 2).

Chemical content

Twenty-six products were test purchased multiple times from different webshops and analysed by the different country laboratories. The average purity (%) values of 24 NPS powders is shown in Fig. 1. Most powders showed a relatively high purity of 65% or above, except for pentedrone, 6-APB, AM-2201 and UR-144. Etizolam and 25I-NBOMe were sold in tablet form or on blotters, respectively. The average 25I-NBOMe content on blotters (n=4) was 835 μg/ blotter and the average etizolam content in the tablets (n=8) was 1.03 mg/ tablet. Purity varied considerably per NPS, in contrast to what was advertised on most webshops (>90-99% purity). Purity also differed per country of purchase, with the UK showing the highest purity (>90%) and Poland the lowest (<60%).

The extent of mislabelling was also determined, mislabelling was defined as ‘not containing the advertised substance at all’. Several examples of mislabelled NPS were encountered (Fig. 2). Mainly, 25I-NBOMe, 3-MMC, 3,4-DMMC and 5-APB samples were mislabelled, but contained chemically similar analogues (e.g. 25B/C-NBOMe instead of 25I-NBOMe, 4-MEC instead of 3-MMC, pentedrone instead of 3,4-DMMC and 6-APB instead of 5-APB, respectively). Likewise, most other mislabelled products tended to contain chemically related NPS, but in some cases the detected content differed substantially from what was advertised (e.g. pentedrone instead of AMT or 3-FMC instead of 5-MeO-DALT).

Test purchases in Poland revealed the highest proportion of mislabelling (33%), whereas samples purchased in the UK all corresponded to what was advertised. There were twenty instances whereby a product contained more than one single NPS, which was not advertised as such on the website. In all of the cases, samples primarily contained the advertised NPS, with a small percentage (<15%) of an additional NPS as adulterant.

Price

On average, the price of a NPS product was € 22.73 ± 13.2 (median € 17.43) and some NPS were relatively more expensive compared to others (e.g. methoxphenidine, AMT or 5-EAPB) (Fig. 3). For comparability, it was decided to compare price within the same chemical NPS class. In the three countries that test purchased cathinones, prices differed substantially, with Poland having the relatively lowest price (Table 3). Prices of synthetic cannabinoids also differed between countries of purchase, with the UK having the lowest nominal average price and remaining lowest after PPP adjustment (Table 4). Such adjustment not only reflects the price levels in each of the I-TREND countries (and notably: the prices compared to the nearest substitute substances like alcohol, tobacco and illicit drugs), but also demonstrates NPS availability for a consumer in each country.

Discussion

This study has shown chemical analysis results for 31 different NPS test purchased across 5 different European countries as part of the EU commissioned research project, I-TREND. Contrary to what is often claimed by webshops and often believed by drug users (Carhart-Harris, King, & Nutt, 2011), the study found that not all the test purchased NPS contained the pure, or nearly pure, product as advertised. Sample purity varied highly between the different NPS, possibly reflecting the adjustment to factors like availability or response to (in)stability of the drug market per specific country. As another market "good", purity and price of NPS maybe subject to largely the same processes as illicit substances and follow the same supply-and-demand dynamics (National Research Council, 2010), thereby explaining variation. However, it may also reflect the degree to which certain NPS were already under scrutiny by the Council of the European Union or the World Health Organisation Expert Committee (WHO) (European Commission, 2015; World Health Organization, 2015). For instance, the UK generally showed a high purity of NPS, but this may be due to the fact that none of these substances were the focus of discussion questioning their legality at the time of test purchasing samples for this project (European Commission, 2015; World Health Organization, 2015). In other instances, webshops may have already stopped the sale of certain NPS in the wake of forthcoming legislation (e.g. 25I-NBOMe, MDPV or methoxetamine). These matters left aside, differences in purity might also reflect an attempt to provide good quality products and to remain competitive in a highly dynamic and quickly changing market like the Internet.

Secondly, the results of this study highlight that a considerable proportion of NPS was mislabelled by the webshops. In most instances, highly similar NPS analogues were sold instead of the specific compounds advertised. For example, samples contained pentedrone instead of ethylcathinone. But in some cases, the contents was entirely different to the one advertised. This may lead to users ingesting substances with unanticipated effects and possibly different effective doses, which can cause serious harm. For instance, α-PVP is a much more potent stimulant than 4-FA and it was present in one sample advertised as 4-FA. In previous research mislabelling of street drugs has been shown multiple times with fatal consequences. For instance, acetyl fentanyl being sold as heroin (McIntyre, Trochta, Gary, Wright, & Mena, 2016; Stogner et al., 2014), paramethoxymethamphetamine (PMMA) or paramethoxyamphetamine (PMA) being sold as ecstasy/amphetamine (Dams et al., 2003; Martin, 2001; Vevelstad et al., 2012) or 4-methylamphetamine being sold as amphetamine

(Blanckaert et al., 2013). But research directed at the online NPS market has also seen instances of mislabelling which may be a cause for concern (Baron, Elie, & Elie, 2011; Elie, Elie, & Baron, 2013; McLaughlin et al., 2015; Zuba, Byrska, & Maciow, 2011).

The mislabelling of NPS products calls for rigorous monitoring of the drug market through international pharmacovigilance, through systems such as the European Union Early Warning System (EMCDDA Europol, 2007). Some countries have implemented drug testing services to inform consumers and health care professionals, such as the DIMS in the Netherlands, WEDINOS in the UK and SINTES in France (Brunt et al., 2016; Brunt & Niesink, 2011; Giraudon & Bello, 2009; NHS Wales, 2015), about mislabelled, high-dosed or adulterated drugs. This may prevent dangerous substances from circulating on the streets and vendors withdrawing unwanted products more rapidly. One example of this occurred in the UK when 5-IT was withdrawn from sales after it transpired that this compound was associated with severe adverse events, including deaths (European Monitoring Centre for Drugs and Drug Addiction, 2014b). Subsequently, this was followed by subjecting this substance to a ban (The Council of The European Union, 2013).

Recent case reports have described the NBOMe-series of drugs being sold as LSD or 2C-B (Gee, Schep, Jensen, Moore, & Barrington, 2016; Walterscheid et al., 2014), drugs that are pharmacologically active in different doses or administration routes. Individuals have been taking excessive doses of 25B-NBOMe, a much more potent substance, based on the believed purchase of 2C-B, resulting in hospital admissions due to severe adverse events (Gee et al., 2016). 25I-NBOMe has also been sold as LSD and this has led to unfortunate incidents in the past (Kueppers et al., 2015; Shanks, Sozio, & Behonick, 2015; Walterscheid et al., 2014). The doses of 25B/C/I-NBOMe that were found on the blotters in the present study were usually considerably higher than equivalent doses of LSD on a blotter. Here, an average dose of 835 μg/ blotter (maximum 1575 μg) 25I-NBOMe was detected. Comparable doses were found in another recent toxicological study where several NBOMe derivatives were found on blotters (ranging from 510 μg 25C-NBOMe to 1500 μg 25B-NBOMe) (Poklis, Raso, Alford, Poklis, & Peace, 2015). Although detailed clinical studies are not available to assess dose-response effects in humans, it has become increasingly clear that the toxicity associated with the known NBOMe derivatives is substantial (European Monitoring Centre for Drugs and Drug Addiction, 2014a; Hieger et al., 2015).

The present study also showed a great variety in price between the different NPS and the 5 I-TREND countries involved. Poland showed substantially lower prices of cathinones per

gram than the Netherlands or Czech Republic. Conceivably, this might be a direct reflection of the economic and welfare status, given that the average annual wage in Poland is much lower than that of the other countries participating in this study (International Labour Organization, 2015). Interestingly, nominal and PPP-adjusted prices of synthetic cannabinoids were substantially lower in the UK than in the other countries, which might be due to the legal status of these substances selected by the UK at the time of this project (European Commission, 2015; World Health Organization, 2015). As the sale of NPS probably happens from common suppliers throughout the globe, the controlling of some of the substances in the UK (e.g. methoxetamine, 25I-NBOMe, 6-APB) at the time of this study might have led to shifts in price in surrounding countries, like France or The Netherlands, since shipment to the UK was no longer an option.

The absence of synthetic cannabinoids in the Netherlands might be the consequence of the liberal cannabis policy of the Netherlands, making good quality herbal cannabis widely available and suppressing the need for synthetic alternatives (MacCoun, 2011). The present results have revealed that two countries with a large NPS market (Poland and UK) offer very different quality of NPS. In Poland, despite the introduction of the blanket ban in 2010, the NPS market re-emerged in 2014 (Malczewski et al., 2015), with 100 brick and mortar stores. However, this has led to Poland having the highest amount of mislabelled NPS in this study. By contrast, in the UK the amount of mislabelled NPS was lowest. Moreover, the NPS purity levels were on the two extremes in these countries.

It is important to note that the UK has adopted a new Psychoactive Substances Act starting in 2016 and this may have impacted on price and purity of the different NPS in this current study greatly since the Act has come into action (The Stationery Office, 2016). It was predicted by the UK Home Office that this Act will end the legal sale of NPS from street retailers and UK-based websites. The possibility of a displacement effect to purchasing from the dark web, the domestic black market and purchasing NPS from international retailers, is a worthy consideration. It has to be mentioned that a large proportion of UK webshops was already hosted in the United States at the time of this study and this proportion might have conceivably grown since the new Psychoactive Substances Act (European Monitoring Centre for Drugs and Drug Addiction, 2016b). The impact of the Act has yet to be evaluated, but research exploring the impact of the Act on both the UK domestic market, and the European NPS market, would be a worthwhile follow-up study and a useful case study to explore the impact of legalisation in one country on the NPS market on others.

In an international multi-centre study like this there are some inherent shortcomings to consider. First of all, there were country-specific differences in webshops, some webshops were easily accessible and the ordering of substances unproblematic, but others were unreliable and did not ship the products ordered or did not ship to specific EU countries, which challenged some participating institutions. This caused for incomplete analyses and missing results. Secondly, in parallel with the running time of this project the Council of the European Union or the World Health Organisation (WHO) Expert Committee were working on legislative action towards certain NPS that had been selected by participating institutions to include for analysis. Reference standards for these NPS had already been ordered, but availability through Internet suddenly changed after the announcement of the bans. It is also important to bear in mind that whereas the webshops selected in this study were directed at the population of different countries, these webshops are hosted by international (and sometimes untraceable) servers and the products they offer are by no means necessarily in stock at a particular location, but rather on wholesale stock somewhere else (Grund, Vavrincikova, Fidesova, & Janikova, 2016). NPS trade takes place on a global level, which means that shops are merely offering what they believe is in demand or what is in stock at that time. National legislative action is likely to have a decisive impact on what NPS are offered through country-specific webshops.

Also, some laboratory techniques have a higher sensitivity than others, so detection of minute concentrations of NPS is expected to vary between laboratories. This may have resulted in an underreporting of certain NPS or adulterants. The same applies to the use of spectral libraries, since more complete and current spectral libraries are expected to translate to greater detection rates and fewer false negatives. It is recommendable to have inter-laboratory validation in the future to prevent erroneous results.

Conclusion

Taken together, the current study provides a snapshot of the purity, composition and price of NPS that were available between 2014-2015 in webshops directed at different European countries. Despite the fact that effects of most NPS are still poorly understood, it is clear that there is a potential danger of mislabelling or adulteration of these substances. This is an important consideration for those working in the field of acute prevention and addiction care. The present findings are important to those studying the drug market in general by helping to understand how different NPS are marketed in different countries and the great variety in

price and purity of delivered products, which might be the result of the complex interaction of market dynamics and the role of law enforcement.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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Table 1

The 31 NPS that were selected and test purchased for this study, abbreviations, chemical classes and main effect are given.

NPS Chemical class	Chemical name	Main abbreviation (chemical)	Other names	Main effect
Aminoindanes	2-Aminoindane	2-AI[#]		Stimulant
	N-Methyl-2-aminoindane	NM-2-AI[#]		Stimulant
Arylalkylamines	5-(2-Aminopropyl)indole	5-IT	5-API	Stimulant/ Hallucinogen
	5-(2-Aminopropyl)benzofuran	5-APB	Benzofury	Entactogen
	6-(2-Aminopropyl)benzofuran	6-APB	Benzofury	Entactogen
	1-(Benzofuran-5-yl)-*N*-ethylpropan-2-amine	5-EAPB[#]		Entactogen
	Methiopropamine	MPA		Stimulant
Arylcyclohexylamines	Methoxetamine	MXE	Mexxy, M-ket	Dissociative
Benzodiazepines	Etizolam	Etizolam	Etilaam, Etizest	Depressant
Cathinones	3-Chloromethcathinone	3-CMC	Meta-clephedrone	Stimulant
	3,4-Dimethylmethcathinone	3,4-DMMC		Stimulant
	3-Methylmethcathinone	3-MMC		Stimulant
	4-Methyl-*N*-ethcathinone	4-MEC	NRG-2	Stimulant
	α-Pyrrolidinopentiophenone	α-PVP	Flakka	Stimulant
	Ethcathinone	ETH-CAT	Ethcathinone	Stimulant
	3,4-Methylenedioxypyrovalerone	MDPV	NRG-1	Stimulant
	4-Methyl-α-pyrrolidinopropiophenone	MPPP		Stimulant
	4-Bromomethcathinone	4-BMC	Brephedrone	Stimulant
	α-Methylamino-valerophenone		Pentedrone	Stimulant
Diarylethylamines	Methoxphenidine	MXP[#]		Dissociative
Indolalkylamines	5-Methoxy-*N*,*N*-diallyltryptamine	5-MeO-DALT[#]		Hallucinogen
	α-Methyltryptamine	AMT	3-IT	Stimulant/ Hallucinogen

Phenethylamines	2-Fluoromethamphetamine	2-FMA		Stimulant
	4-Fluoroamphetamine	4-FA	Flux, 4-FMP	Stimulant
	Ethylphenidate	EPH		Stimulant
	2-(4-Iodo-2,5-dimethoxyphenyl)-*N*-[(2-methoxyphenyl)methyl] ethanamine	25I-NBOMe	N-bomb, Cimbi-5	Hallucinogen
Synthetic cannabinoids	*N*-(adamantan-1-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide	5F-AKB48[#]	5F-APINACA	Cannabis-like
	1-Pentyfluoro-1*H*-indole-3-carboxylic acid 8-quinolinyl ester	5F-PB22		Cannabis-like
	N-(Adamantan-1-yl)-(1-pentyl)-1*H*-indazole-3-carboxamide	AKB48	APINACA	Cannabis-like
	1-(5-Fluoropentyl)-3-(1-naphthoyl)indole	AM-2201		Cannabis-like
	(1-Pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone	UR-144	YX-17	Cannabis-like

[#] These were follow-up substances after the UK ban of substances initially selected.

Table 2
The list of different NPS products that were obtained by the different partner countries (number of purchases is given).

Substance name (NPS)	The Netherlands *N*	United Kingdom *N*	France *N*	Poland *N*	Czech Republic *N*	Total *N*
2-AI*	0	8	0	0	0	8
2-FMA	0	0	0	0	2	2
3-CMC	0	0	0	0	1	1
3-MMC	3	0	0	2	3	8
3,4-DMMC	0	0	0	3	0	3
4-FA	9	0	0	0	0	9
4-MEC	4	0	0	0	0	4
5-APB	1	0	4	0	0	5
6-APB	6	0	3	0	0	9
5-EABP*	1	8	0	0	0	9
5F-AKB-48	0	8	0	0	0	8
5F-PB-22	0	0	0	0	2	2
5-IT	2	0	0	0	0	2
5-MeO-DALT*	0	8	3	0	0	11
25I-NBOMe	5	0	1	0	0	6
α-PVP	0	0	0	2	2	4
AKB-48	0	4	0	0	0	4
AM-2201	0	0	2	2	1	5
AMT	0	8	0	0	1	9
Brephedrone	0	0	0	1	0	1
Ethcathinone	0	0	0	4	0	4
Ethylphenidate	0	8	4	0	3	15
Etizolam	0	8	0	0	0	8
MDPV	4	0	0	0	0	4
Methoxetamine	6	0	0	0	0	6
Methoxphenidine*	0	8	0	0	0	8
MPA	0	8	0	0	1	9
MPPP	0	0	0	1	0	1
N-Methyl-2AI*	0	8	0	0	0	8
Pentedrone	0	0	0	2	3	5
UR-144	0	0	2	2	0	4
Total	41	84	19	19	19	182

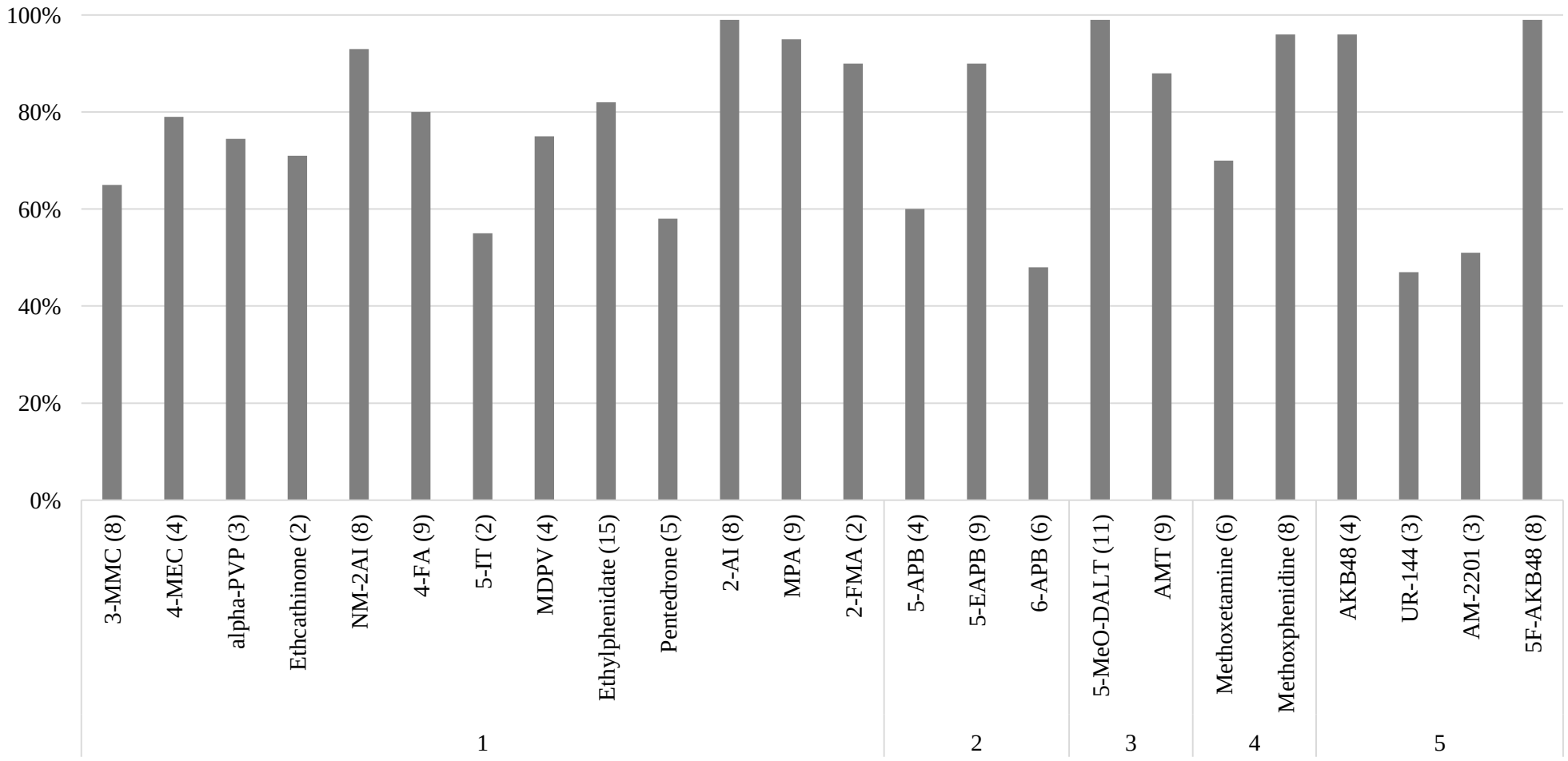
* These were follow-up substances after the UK ban of substances initially selected.

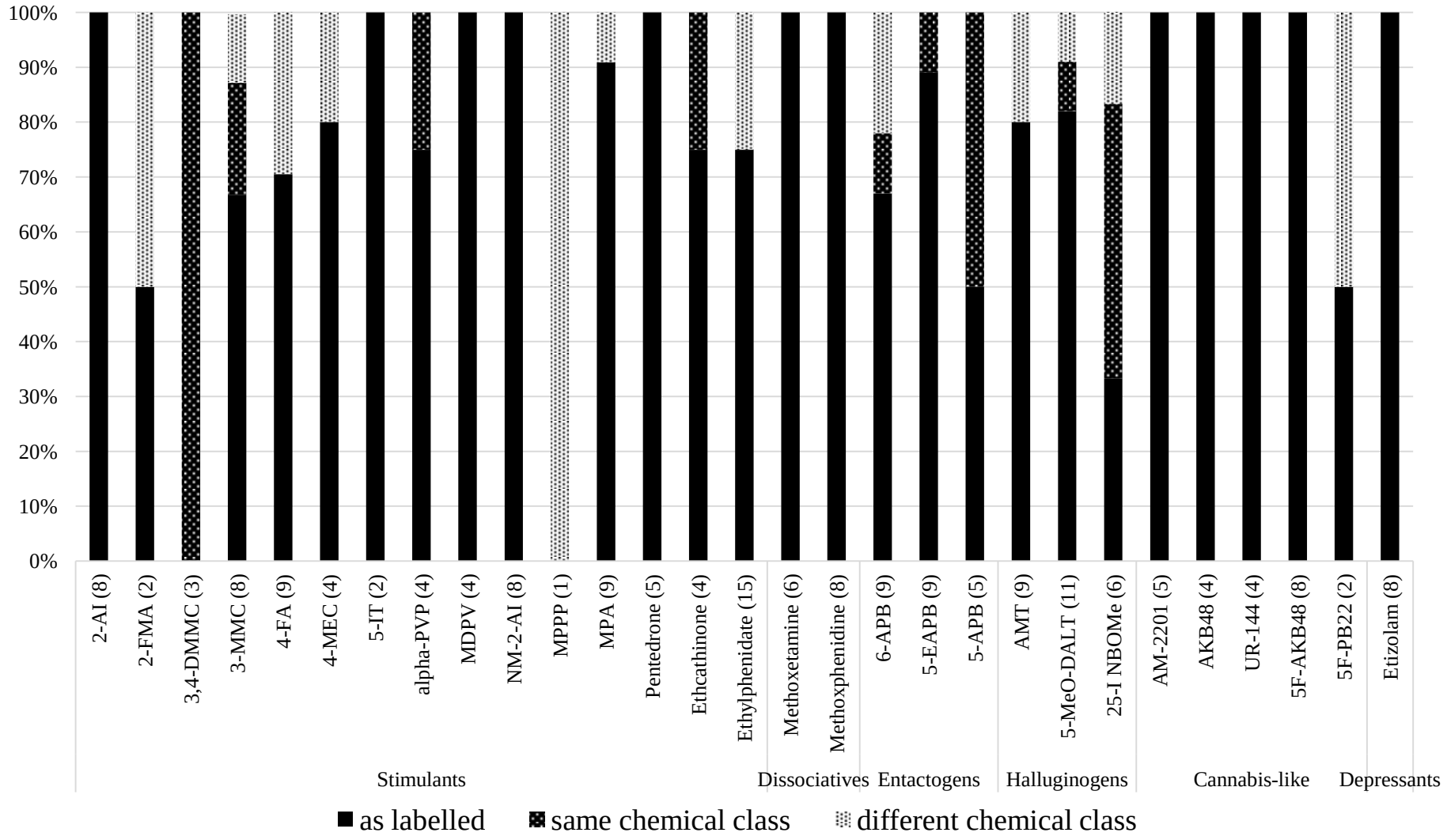
Table 3
Synthetic cathinone prices per country (EUR), given in absolute, purity adjusted and purchased power parities (PPPs).

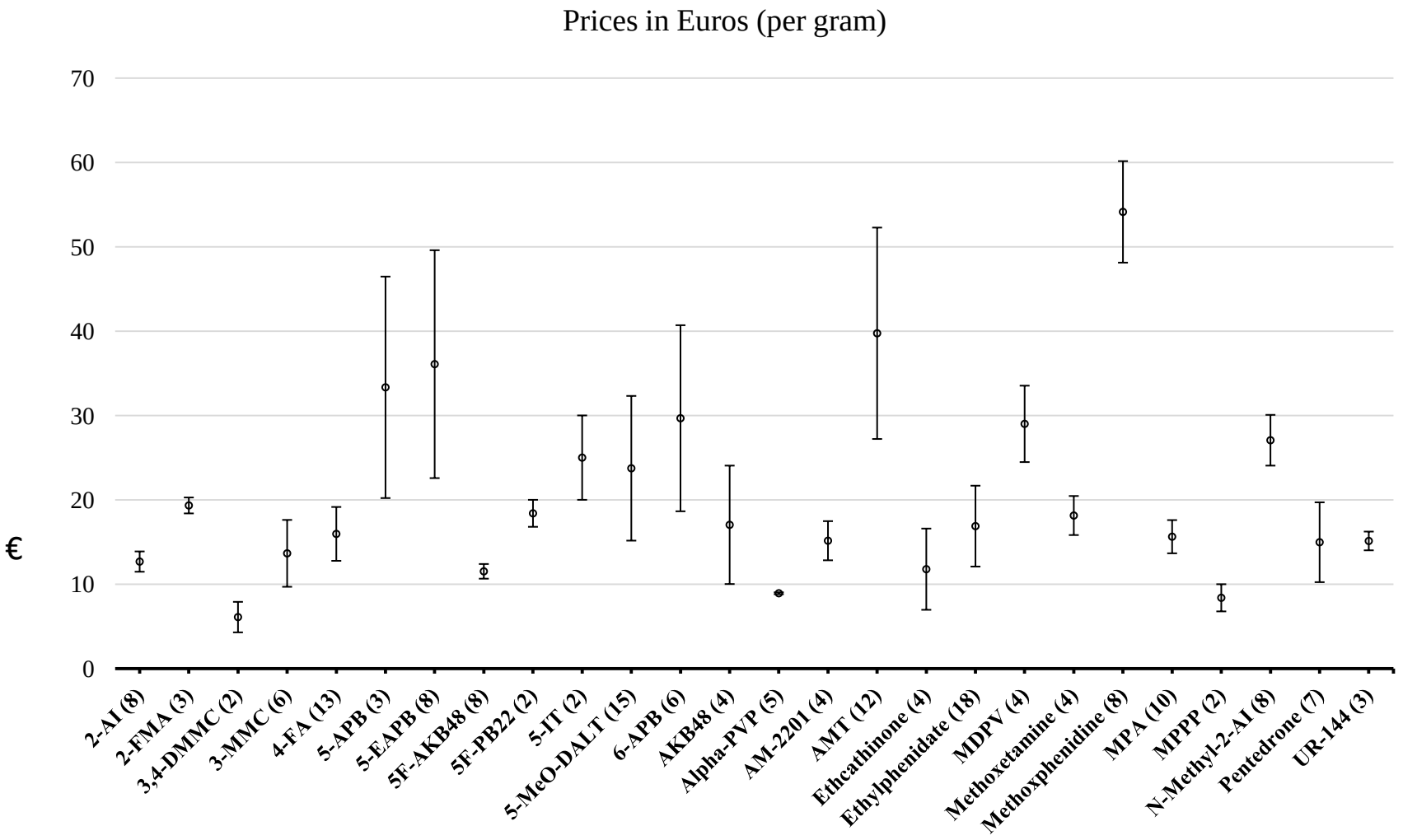
	The Netherlands		Poland		Czech Republic	
	Price per gram	PPP adjusted	Price per gram	PPP adjusted	Price per gram	PPP adjusted
	23,84	22,05	8,33	12,54	16,47	25,45
purity adjusted	33,58	31,05	14,12	21,26	19,60	30,29
stdv	6,07	5,62	2,06	3,07	4,13	11,47

Table 4
Synthetic cannabinoid prices per country (EUR), given in absolute, purity adjusted and purchased
power parities (PPPs).

	United Kingdom		France		Poland		Czech Republic	
	Price per gram	PPP adjusted	Price per gram	PPP adjusted	Price per gram	PPP adjusted	Price per gram	PPP adjusted
price	11,36	7,07	16,00	15,08	14,12	21,05	18,10	26,76
purity adjusted	12,08	7,52	24,62	23,20	23,94	35,69	21,55	31,86
stdv	0,95	0,59	-	-	1,87	2,79	1,37	2,02


Purity per NPS
100%
80%
60%
40%
20%
0%
3-MMC (8)
4-MEC (4)
alpha-PVP (3)
Ethcathinone (2)
NM-2AI (8)
4-FA (9)
5-IT (2)
MDPV (4)
Ethylphenidate (15)
Pentedrone (5)
2-AI (8)
MPA (9)
2-FMA (2)
5-APB (4)
5-EAPB (9)
6-APB (6)
5-MeO-DALT (11)
AMT (9)
Methoxetamine (6)
Methoxphenidine (8)
AKB48 (4)
UR-144 (3)
AM-2201 (3)
5F-AKB48 (8)
1
2
3
4
5


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
2-AI (8)
2-FMA (2)
3,4-DMMC (3)
3-MMC (8)
4-FA (9)
4-MEC (4)
5-IT (2)
alpha-PVP (4)
MDPV (4)
NM-2-AI (8)
MPPP (1)
MPA (9)
Pentedrone (5)
Ethcathinone (4)
Ethylphenidate (15)
Methoxetamine (6)
Methoxphenidine (8)
6-APB (9)
5-EAPB (9)
5-APB (5)
AMT (9)
5-MeO-DALT (11)
25-I NBOMe (6)
AM-2201 (5)
AKB48 (4)
UR-144 (4)
5F-AKB48 (8)
5F-PB22 (2)
Etizolam (8)
Stimulants
Dissociatives
Entactogens
Halluginogens
Cannabis-like
Depressants
as labelled
same chemical class
different chemical class


Prices in Euros (per gram)
€
70
60
50
40
30
20
10
0
2-AI (8)
2-FMA (3)
3,4-DMMC (2)
3-MMC (6)
4-FA (13)
5-APB (3)
5-EAPB (8)
5F-AKB48 (8)
5F-PB22 (2)
5-IT (2)
5-MeO-DALT (15)
6-APB (6)
AKB48 (4)
Alpha-PVP (5)
AM-2201 (4)
AMT (12)
Ethcathinone (4)
Ethylphenidate (18)
MDPV (4)
Methoxetamine (4)
Methoxphenidine (8)
MPA (10)
MPPP (2)
N-Methyl-2-AI (8)
Pentedrone (7)
UR-144 (3)

Legends to figures:

Fig. 1. Average purity of NPS detected over multiple webshop test purchases, number is depicted between brackets. Substances by effect, stimulants (1), entactogens (2), hallucinogens (3), dissociatives (4), cannabis-like (5).

Fig. 2. Products test purchased online which contained the NPS as labelled or contained a NPS of the same chemical class or contained a NPS of a different chemical class.

Fig. 3. Average prices of NPS products per gram, number of purchases is depicted between brackets. These price were not adjusted for purity, since some products did not contain the advertised compound. Error bars represent ± standard deviation.

Table S5

Overview of laboratory* methods utilized by the different partner countries.

METHODS	France	Poland	Czech Republic	UK	Netherlands
(LC/ESI/QToF)	√	√			
(LC/ESI/MS/MS)	√	√			√
(LC/ESI/MS)	√	√	√	√	√
(LC/DAD)	√	√	√	√	√
GC/FID)	√	√	√	√	√
(GC/MS)	√		√	√	√
(GC/MS/MS)	√		√		

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Statement 1: Conflict of Interest

All authors declare that they have no conflicts of interest.

Statement 2: Role of Funding Sources

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Statement 3: Contributors

Authors Tibor Brunt and Simon Brandt designed the study. All co-authors collected the data and Tibor Brunt analysed the data and compiled the manuscript. Author Tibor Brunt wrote the manuscript, did the editing, formatting, citations. Vendula Belackova did the price analyses. All authors revised, contributed to and have approved the final manuscript.