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Mortality involving New Psychoactive Substances across Europe, 2016-2017 ☆

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ABSTRACT

Background-Aims: New psychoactive substances (NPS) are new narcotic or psychotropic drugs that are not controlled by the drug conventions of the United Nations. In the last 10 years, numerous NPS have been identified in Europe but there is no comprehensive overview of mortality related to them. This study aims to estimate the mortality related to NPS in Europe in 2016 and 2017.

Methods: The number of drug-related deaths (DRD) 2016-2017 was retrieved from a) the annual national reports of European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) countries (Statistical Bulletin (2018/2019) and 'Harms and harm reduction workbooks' (2017/2018)) and b) EMCDDA Risk Assessment Reports of the EU Early Warning System on several specific NPS (2017-2018). Population data was retrieved from Eurostat (2016/2017). Incidence of DRD and of DRD involving at least one NPS was calculated.

Findings: Of all DRD recorded in Europe, 11.7% in 2016 and 18.1% in 2017 involved at least one NPS (NPS-DRD), from 2.7 to 4.9 deaths per million of 15 to 64-year-old inhabitants. Between 2016 and 2017, a significant increase was observed (30%, odds ratio 1.33, CI95% 1.26-1.45, $p < 0.0001$) and in particular, DRD involving novel benzodiazepines, novel opioids and synthetic cannabinoids ($p < 0.0001$). In 2016 and2017, 72.8% and 76.8% of cases were concentrated in the UK and Turkey (combined), related mainly to Etizolam and synthetic cannabinoids respectively.

Interpretation: In 2017, one in six drug-related deaths in Europe involved NPS, and the proportion and numbers increased from 2016 levels, although three out of four cases were concentrated in only two countries and a few substances. To fully understand the public health implications of NPS, further monitoring on NPS-DRD and their distribution in Europe is needed.

1. Background

Recent years have witnessed the arrival of a wide variety of new psychoactive substances (NPS) on Europe's illicit drug market. Some of these substances are highly potent and have been associated with acute harms and in some cases drug-related deaths (DRDs).

Several names for the same drug-market development have been coined: 'Designer drugs', 'legal highs', 'new psychoactive substances', 'novel drugs' or 'new psychoactive drugs' King, 2011. NPS is the preferred term of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (COUNCIL DECISION 2019). While the term NPS is used to describe many substances that have emerged in the drug market over the last 20 years or so, the term is not related to any intrinsic chemical or pharmacological properties of the substance. The formal inclusion of a substance in the NPS definition is time-dependent (based on legal status) (Peacock et al., 2019). A recent pragmatic definition by Peacock et al (2019) defines NPS as "narcotic drugs or psychotropic

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substances made available or used from the early to mid-2000s for their psychoactive properties“ (Peacock et al., 2019). For this study, the formal EMCDDA definition has been adapted for practical purposes (see the section on NPS definition). The appearance of NPS has been closely monitored by the EMCDDA-Europol Early Warning System (EWS). Until 2019, over 800 unique NPS were reported to the EWS of the EMCDDA and Europol, of which more than half had been reported since 2014 (Peacock et al., 2019).

Mortality directly caused by drugs (“drug-related deaths, DRD” according to EMCDDA definition) is arguably the most important drug-related harm that is monitored. These data also play a key role in risk assessments (COUNCIL DECISION 1999, Nutt et al., 2010), cost of illegal drugs assessments (Barrio et al., 2017), epidemiological studies (Walker et al., 2017) and policy discussions. In 2018, there were at least 8300 DRDs in the 28 EU Member States and at least 9200 when including Norway and Turkey (COUNCIL DECISION 2020). Preliminary data for 2019 suggest a stable number (COUNCIL DECISION 2020). Indeed, reduction of DRDs is a priority for European governments, the European Commission, the EMCDDA, the World Health Organisation and the United Nations (EMCDDA 2019, Cao et al., 2018, United Nations 2012).

There is a lack of epidemiological studies presenting an overview of the overall mortality related to NPS in the European population (deaths caused by NPS themselves or deaths where NPS played a role in the outcome). Although some studies, such as risk assessments, have reported mortality related to NPS in a specific country or region (McAuley et al., 2015) or for a specific type of NPS (Riederer et al., 2016), until now there has been no assessment of deaths involving NPS in Europe per year, and this is essential for an epidemiological and public health assessment (Peacock et al., 2019).

In this paper, overall European figures for deaths associated with NPS belonging to different substance types are presented; these figures have been retrieved from a variety of different, complementary sources. The NPS categories studied in this paper include synthetic cannabinoid receptor agonists, synthetic cathinones, novel benzodiazepines, and opioids. Synthetic cannabinoids (SC) include substances that act on the cannabinoid receptors, mimicking the effects of cannabis; they have been associated, in some cases, with severe adverse events (stroke, seizure, myocardial infarction, rhabdomyolysis, acute kidney injuries, psychosis) (Tait et al., 2016, Dines et al., 2015, Vallersnes et al., 2016, Wolfe et al., 2019). Cathinones, novel benzodiazepines and synthetic opioids have also been linked to harms and deaths in some cases. In particular, fentanyl derivatives pose a life-threatening risk of poisoning from respiratory depression (Kraemer et al., 2019). The EMCDDA plays a key role in assessing and responding to substances that may pose severe public health and social risks in Europe. For the substances that undergo a risk assessment, Member States are required to provide all the data available on the substance under scrutiny. Therefore, at the stage of risk assessment, the information available for each of these substances is very comprehensive. This information includes a detailed account of all the serious adverse events that occurred in the Member States, including deaths, where there is an analytically confirmed exposure to the substance.

However, despite the efforts invested in the early warning and risk assessment area, there are no population-based epidemiological studies of NPS-DRD in Europe. This means that there is not yet reliable information on the number of those deaths in Europe as a whole, where they occur, and which substances are involved. This lack of information has created a serious gap in the definition of European and national drug strategies, including priority for actions, research, and monitoring.

This study aims to describe, for the first time, the overall mortality related to NPS in Europe, the limitations and strengths of the current approach to registering these deaths, and gaps in the research of NPS-DRD.

The information obtained in this study will identify the real population scale of deaths with presence of NPS, and the profiles of these deaths, in terms of geographical distribution, population groups affected and the main substances actually involved in most deaths, and in combination with which deaths. This will allow the formulation of interventions (harm-reduction, guidelines for practitioners in emergency services) based on reliable and relevant information in each jurisdiction.

2. Methods

2.1. Sources of information (supplementary material 1)

EMCDDA Statistical Bulletin – overdose deaths: reports from the National Focal Points (Reitox) of the EU 28 Member States – including the United Kingdom that was a Member State of the EU during the timeframe covered in the study – Norway and Turkey, from 2018 and 2019 (United Nations 2018a, b, 2019).

Drug-related harms and harm reduction workbooks reported in 2017 and 2018 (structured annual report of the National Focal Points).

Risk assessment reports of NPS conducted in 2017 and 2018 (EU Early Warning System, EMCDDA) (United Nations 2021).

2.2. Definition of drug-related deaths (DRD)

The EMCDDA case definition of DRD includes “deaths happening shortly after consumption of one or more illicit psychoactive drugs, and directly related to this consumption” although they may often happen in combination with other substances such as alcohol or psychoactive medicines (United Nations 2010). These deaths are often called overdoses or poisonings and, in some cases “drug-induced deaths”.

2.3. Definition of NPS

A new psychoactive substance (NPS) is defined as a new narcotic or psychotropic drug, in pure form or preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions. (United Nations 2019, United Nations 2017)

NPS is a legal definition established for the control of drugs, but not a medical or epidemiological classification. However, the definition compares NPS to drugs that are controlled internationally based on their public health risks, prevalence and/or medical use. For this research, NPS are substances that have been identified through the European Union Early Warning System regardless of whether they have subsequently been put under international control. Ketamine and GBL (not controlled) are included, as well as GHB (only controlled in 2001). In this paper, the following categories of NPS were included as those identified in the reported NPS-DRD cases: novel opioids, novel benzodiazepines, Ketamine, GHB/GBL, synthetic cathinones and other novel stimulants, novel hallucinogens, and synthetic cannabinoids.

2.4. Countries

Data from countries that reported information on DRD in 2016 and 2017 to the EMCDDA in the Harms and harm reduction workbooks 2017 and 2018 edition and in the Statistical Bulletin –overdose deaths were included. Twenty-seven countries were included in 2016 and twenty-four in 2017 (see Tables 1 and 2).

2.5. Analyses

We retrieved or calculated the following variables for 2016 and 2017, for Europe and individual countries:

1. The total number of DRD, and whether toxicology was reported; the rate of DRD per million inhabitants, and the rate per million inhabitants aged between 15 and 64, with and without reported toxicology.

Table 1
Number and incidence of DRD. DRD with toxicology and DRD involving at least one NPS in 2016.

2016	Population	Population 15-64 y.o.	Total DRD	Total DRD per million inhab.	Total DRD per 100,000 inhab. (15-64 y.o.)	Total DRD with toxicology	Total DRD with toxicology per million inhab.	Total DRD with toxicology per million inhab. (15-64 y.o.)	Total DRD involving NPS	% NPS-DRD out of total DRD with toxicology	Total DRD involving NPS per million inhab.	Total DRD involving NPS per million inhab. (15-64 y.o.)
Austria	8700471	5846717	165	19.0	28.2	140	16.1	23.9	3	2.1	0.3	0.5
Belgium	11311117	7329604	60	5.3	8.2	60	5.3	8.2	5	8.3	0.4	0.7
Croatia	4190669	2774223	56	13.4	20.2	36	8.6	13.0	0	0.0	0.0	0.0
Cyprus	848319	580250	6	7.1	10.3	6	7.1	10.3	0	0.0	0.0	0.0
Czech Republic	10553843	6997198	32	3.0	4.6	32	3.0	4.6	0	0.0	0.0	0.0
Denmark	5707251	3669762	237	41.5	64.6	232	40.7	63.2	0	0.0	0.0	0.0
Estonia	1315944	854048	114	86.6	133.5	114	86.6	133.5	24	21.1	18.2	28.1
Finland	5487308	3467979	194	35.4	55.9	194	35.4	55.9	34	17.5	6.2	9.8
France	66638391	41782271	406	6.1	9.7	406	6.1	9.7	16	3.9	0.2	0.4
Germany	82175684	53989424	1333	16.2	24.7	1333	16.2	24.7	76	5.7	0.9	1.4
Greece	10783748	6923166	73	6.8	10.5	31	2.9	4.5	0	0.0	0.0	0.0
Hungary	9830485	6606086	29	3.0	4.4	29	3.0	4.4	13	44.8	1.3	2.0
Italy	60665551	39007949	268	4.4	6.9	149	2.5	3.8	0	0.0	0.0	0.0
Latvia	1968957	1281791	18	9.1	14.0	18	9.1	14.0	0	0.0	0.0	0.0
Lithuania	2888558	1918003	109	37.7	56.8	109	37.7	56.8	0	0.0	0.0	0.0
Luxembourg	576249	399917	5	8.7	12.5	5	8.7	12.5	0	0.0	0.0	0.0
Malta	450415	303580	5	11.1	16.5	5	11.1	16.5	0	0.0	0.0	0.0
Norway	5210721	3423444	282	54.1	82.4	282	54.1	82.4	0	0.0	0.0	0.0
Poland	37967209	26197374	204	5.4	7.8	47	1.2	1.8	7	14.9	0.2	0.3
Portugal	10341330	6732206	30	2.9	4.5	27	2.6	4.0	1	3.7	0.1	0.1
Romania	19760585	13239592	19	1.0	1.4	19	1.0	1.4	4	21.1	0.2	0.3
Slovenia	2064188	1376813	40	19.4	29.1	35	17.0	25.4	0	0.0	0.0	0.0
Spain	46440099	30696905	613	13.2	20.0	501	10.8	16.3	0	0.0	0.0	0.0
Sweden	9851017	6186439	590	59.9	95.4	567	57.6	91.7	92	16.2	9.3	14.9
The Netherlands	16979120	11087365	235	13.8	21.2	235	13.8	21.2	3	1.3	0.2	0.3
Turkey	78741053	53386434	920	11.7	17.2	890	11.3	16.7	377	42.4	4.8	7.1
UK	65379044	42038725	3256	49.8	77.5	3256	49.8	77.5	367	11.3	5.6	8.7
Europe	576827326	378097265	9299	16.1	24.6	8758	15.2	23.2	1022	11.7	1.8	2.7

EU countries not included: Bulgaria, Ireland and Slovakia

Table 2
Number and incidence of DRD. DRD with toxicology and DRD involving at least one NPS in 2017.

2017	Population	Population 15-64 y.o.	Total DRD	Total DRD per million inhab.	Total DRD per million inhab. (15-64 y.o.)	Total DRD with toxicology	Total DRD with toxicology per million inhab.	Total DRD with toxicology per million inhab. (15-64 y.o.)	Total DRD involving NPS	% NPS-DRD out of total DRD with toxicology	Total DRD involving NPS per million hab.	Total DRD involving NPS per million hab. (15-64 y.o.)
Austria	8772865	5886592	154	17.6	26.2	122	13.9	20.7	11	9.0	1.3	1.9
Belgium	11351727	7333216	62	5.5	8.5	62	5.5	8.5	10	16.1	0.9	1.4
Bulgaria	7101859	4630412	18	2.5	3.9	18	2.5	3.9	0	0.0	0.0	0.0
Croatia	4154213	2733472	65	15.6	23.8	65	15.6	23.8	0	0.0	0.0	0.0
Cyprus	854802	582975	16	18.7	27.4	16	18.7	27.4	0	0.0	0.0	0.0
Czech Republic	10578820	6950285	42	4.0	6.0	42	4.0	6.0	1	2.4	0.1	0.1
Denmark	5748769	3690710	254	44.2	68.8	254	44.2	68.8	0	0.0	0.0	0.0
Estonia	1315635	848585	110	83.6	129.6	110	83.6	129.6	26	23.6	19.8	30.6
Finland	5503297	3461574	200	36.3	57.8	200	36.3	57.8	34	17.0	6.2	9.8
Germany	82521653	53969161	1272	15.4	23.6	960	11.6	17.8	75	7.8	0.9	1.4
Greece	10768193	6891644	62	5.8	9.0	31	2.9	4.5	0	0.0	0.0	0.0
Hungary	9797561	6544771	33	3.4	5.0	33	3.4	5.0	14	42.4	1.4	2.1
Italy	60589445	38837834	294	4.9	7.6	220	3.6	5.7	2	0.9	0.0	0.1
Latvia	1950116	1259775	22	11.3	17.5	22	11.3	17.5	0	0.0	0.0	0.0
Lithuania	2847904	1876769	83	29.1	44.2	83	29.1	44.2	7	8.4	2.5	3.7
Luxembourg	590667	411104	8	13.5	19.5	8	13.5	19.5	0	0.0	0.0	0.0
Malta	460297	308399	5	10.9	16.2	5	10.9	16.2	0	0.0	0.0	0.0
Portugal	10309573	6680603	38	3.7	5.7	38	3.7	5.7	0	0.0	0.0	0.0
Romania	19644350	13102781	32	1.6	2.4	32	1.6	2.4	1	3.1	0.1	0.1
Slovakia	5435343	3777563	19	3.5	5.0	19	3.5	5.0	0	0.0	0.0	0.0
Slovenia	2065895	1367622	47	22.8	34.4	37	17.9	27.1	0	0.0	0.0	0.0
Sweden	9995153	6256966	626	62.6	100.0	615	61.5	98.3	127	20.7	12.7	20.3
Turkey	79814871	54274112	941	11.8	17.3	941	11.8	17.3	565	60.0	7.1	10.4
UK	65844142	42140251	3429	52.1	81.4	3429	52.1	81.4	456	13.2	6.9	10.8
Europe	418017150	273817176	7832	18.7	28.6	7362	17.6	26.9	1329	18.1	3.2	4.9

EU countries not included: France, Ireland, Norway, Poland, Spain and The Netherlands.

2. The total number and rate of DRD per million inhabitants, involving at least one NPS (NPS-DRD) – and where available -the mean age at death.
3. The total number of DRD involving individual, selected NPS (when available).
4. The total number of DRD for each selected type of NPS (novel opioids, novel benzodiazepines, cathinones and other novel stimulants, hallucinogens, synthetic cannabinoids, ketamine and GHB/GBL) (when available).

The population of each country was extracted from Eurostat (1 January 2016 and 1 January 2017). The change between 2016 and 2017 was calculated (increase in absolute number, odds ratio (OR) and 95% confidence intervals (95% CI) for all NPS-DRD and for specific group of NPS-DRD in the population aged 15-64 years old, considering 2016 values as the reference group) for DRD with and without toxicology, DRD involving NPS (NPS-DRD) and DRD of each NPS type.

The OR represents the comparison of the ratios of MPS-DRD to the non-NPS-DRD population between 15 and 64 years olds in 2017 over 2016 . ORs were calculated according to the following formula: (a / b)/ (c / d). In which:

a = drug-related deaths in 2017 (total or specific group of NPS)
b = (total population 15-64 years old in 2017) – (drug-related deaths in 2017)
c = drug-related deaths in 2016 (total or specific group of NPS)
d = (total population 15-64 years old in 2016) – (drug-related deaths in 2016)

The method is described in previous publications (Bland and Altman, 2000). OR and their CI95% were conducted by Medcalc software (R) (https://www.medcalc.org/calc/odds_ratio.php).

We also extracted information from Risk Assessment Reports of the EU Early Warning System (EMCDDA) (28) published in 2016 and 2017. Risk Assessments were conducted on four synthetic cannabinoids and seven novel opioids, all of them derivatives of fentanyl. The following data were retrieved: time, country, number and name of reported substances, total number of DRD, number of deaths (n, %) involving only one NPS, gender (n, %), median age, number of deaths (n, %) in which a) the cause of death was the NPS or NPS were likely to have contributed to death according to the forensic report, and b) number (%) of deaths with Toxicological Significance Score (TSS) =3 (meaning, according to the system developed for EMCDDA risk assessments, that the NPS are cited as the cause of death or are likely to have contributed to death) (Elliott et al., 2018).

2.6. Ethical issues

All data were anonymous and followed the General Data Protection Regulation of the European Commission (United Nations 2016, United Nations 2018). No human or animal subjects directly took part in this research. Approval from an ethical committee was therefore not required.

3. Results

3.1. Year 2016

In total, 8758 DRD with known toxicology were reported (out of 9299 total DRD in 27 reporting countries), of which 1022 (11.7%) involved at least one NPS. Most DRD involving NPS occurred in Turkey (n = 377, 36.9%), the UK (n = 367, 35.9%), Sweden (n = 92, 9.0%) and Germany (n = 76, 7.4%). In ten countries, at least 5% of DRD with toxicology available involved NPS: Turkey (42.4%), Hungary (44.8%), Estonia (21.1%), Romania (21.1%), Finland (17.5%), Sweden (16.2%), Poland (14.9%), the UK (11.3%), Belgium (8.3%) and Germany (5.7%). There were 1.8 NPS-DRD per million inhabitants of countries reporting in 2016 (range 0-18.2), and 2.7 per million inhabitants aged 15-64 (range 0-28.1). Five countries were over the European average incidence of NPS-DRD (Estonia, the UK, Finland, Sweden, and Turkey) (Table 1, Figs. 1 and 2).

The types of NPS most frequently involved were synthetic cannabinoids (n = 412, 40.3%), novel benzodiazepines (n = 285, 27.9%), novel opioids (n = 124, 12.1%) and novel stimulants (n = 72, 7.0%). For the synthetic cannabinoids type, the exact substances involved were not available. The most cited specific drugs in NPS-DRD were etizolam (n = 225, 22%) and GHB (n = 31, 3%).

3.2. Year 2017

In total, 7362 DRD with known toxicology were reported (out of 7832 total DRD in 24 reporting countries), of which 1329 (18.1%) involved NPS. Again, most NPS-DRD occurred in Turkey (n = 565, 42.5%), the UK (n = 456, 34.3%), Sweden (n = 127, 9.6%) and Germany (n = 75, 5.6%). In nine countries, at least 5% of DRD with toxicology available involved NPS: Turkey (60%), Hungary (42.4%), Estonia (23.6%), Sweden (20.7%), Finland (17.0%), Belgium (16.1%), the UK (13.3%), Austria (9%), Lithuania (8.4%) and Germany (7.8%). There were 3.2 NPS-DRD per million inhabitants of countries reporting in 2017 (range 0-19.8) and 4.9 per million inhabitants aged 15-64 (range 0-30.6). Five countries were over the European average incidence of NPS-DRD (Estonia, Finland, the UK, Sweden, and Turkey) (Table 2 and Figs. 1 and 2).

The types of NPS most frequently involved were synthetic cannabinoids (n = 612, 46%), novel benzodiazepines (n = 341, 25.7%), novel opioids (n = 198, 14.9%) and novel stimulants (n = 64, 4.9%). For the synthetic cannabinoids type, the exact substances involved were not available. The most cited specific drugs in NPS-DRD were etizolam (n = 301, 22.6%) and carfentanil (n = 35, 2,6%).

Considering the combination of 2016 and 2017 data, the total number of NPS-DRD reported was 2,351, representing the 14.6% of 16,120 DRD with known toxicology, out of the total of 17,131 DRD reported in the EU (28), Norway and Turkey (at the time of conducting the data collection for this research). The combined 2016-2017 mortality rates resulted in 2.4 deaths per million inhabitants, and 3.6 per million inhabitants aged 15-64, considering the populations of reporting countries in each year.

3.3. Changes from 2016 to 2017

Overall, DRD increased from 24.6 per million inhabitants in 2016 to 28.6 per million inhabitants in 2017. Although the number of countries with available data (workbooks) was lower (from 27 to 24), in 2017 the total number of NPS-DRD reported increased by 30% (from 1022 to 1329). Computation of OR was based on the 22 countries with data both in 2016 and 2017 (reporting 996 cases in 2016 and 1329 cases in 2017). NPS-DRD increased significantly considering the 15-64 age group in 2016 as the reference group (OR 1.33, CI95% 1.23-1.45, z-statistic 6837, $p < 0.0001$). The number of DRD-NPS involving synthetic cannabinoids, novel benzodiazepines and novel opioids increased by 48.5% (n = 200), 16.4% (n = 56) and 59.7% (n = 74), respectively. Considering mortality rate among people between 15-64 years of age, increase in NPS-DRD between 2016 and 2017 were statistically significant for synthetic cannabinoids (OR 1.49 CI95% 1.31-1.68, z-statistic 6013, $p < 0.0001$), novel benzodiazepines (OR 1.20 CI95% 1.03-1.41, z-statistic 2295, $p < 0.0217$) and novel opioids (OR 1.66 CI95% 1.32-2.08, z-statistic 4373, $p < 0.0001$).

Seven countries reported increasing NPS-DRD (Austria +8, Belgium +5, Estonia +2, Hungary +1, Sweden +35, Turkey+188, and the UK +89). Three countries reported NPS-DRD in 2017 but not in 2016 (Lithuania seven cases, Italy two cases and the Czech Republic one case). Three countries reported decreasing NPS-DRD (Germany -1, Portugal -1,

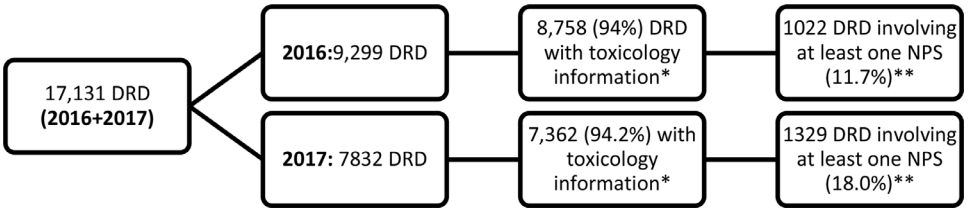

Fig. 1. DRD: Drug-Related Deaths.
NPS: New Psychoactive Substance.
* Sufficient toxicology information available to classify the case in the category with or without opioids.
**Based on the more detailed data reported through the workbooks:
14 out of 27 countries (51.9%) reported at least one DRD involving NPS (DRD-NPS) and 8 countries (29.6%) reported at least 10 during 2016
13 out of 24 countries (54.1%) reported at least one DRD involving NPS (DRD-NPS) and 9 countries (37.5%) reported at least 10 during 2017.

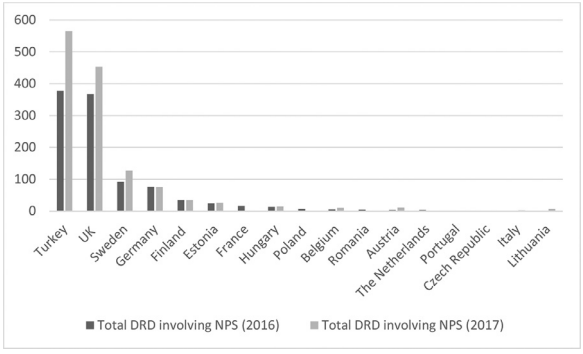

Fig. 2. DRD involving NPS per country.

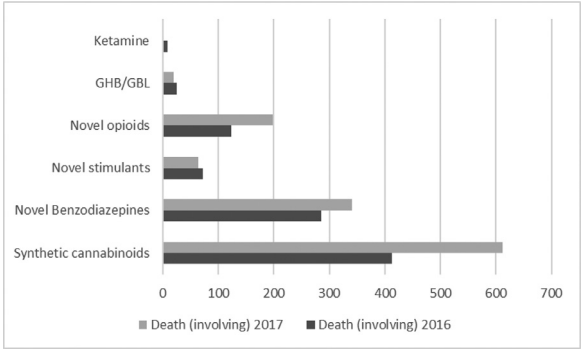

Fig. 3. DRD involving NPS according to the "drug family".

and Romania -3) and 1 country was stable (Finland, $n = 34$). Eight countries reported no cases of NPS-DRD in 2016 or 2017, which accounted for 30.8% of countries reporting 2016 and 33.3% of countries reporting 2017. Considering the 15-64 age group as the reference group, between 2016 and 2017 statistically significant increases in DRD were observed for Austria (OR 3.64, CI95% 1.02-13.05, z-statistic 1.984, p=0.0472), Sweden (OR 1.37 I95% 1.04-1.79, z-statistic 2.272, p=0.0231), the United Kingdom (OR 1.23 CI95% 1.07-1.41, z-statistic 2.963, p=0.0030) and Turkey (OR 1.47 CI95% 1.29-1.68, z-statistic 5.836, $p < 0.0001$). The number of DRD involving NPS according to "drug type" (e.g. novel opioids) is shown in Fig. 3 ("*Substances involved in at least 2 DRD*").

3.4. Additional information from Risk Assessments undertaken by the EU Early Warning System (United Nations 2020)

Eleven Risk Assessments involving seven novel opioids and four synthetic cannabinoids from 13 different countries were conducted between 2017 and 2018. These risk assessments included cases reported between November 2015 and February 2018. Ten countries (Belgium, Czech Republic, Denmark, Estonia, Finland, Germany, Lithuania, Norway, Sweden, and the United Kingdom) reported deaths involving at least one of the novel opioids (all derivatives of fentanyl) subject to risk assessment. Cases involved acryloylfentanyl ($n = 47$ cases) (United Nations 2017), furanylfentanyl ($n = 33$) (United Nations 2017), 4F-iBF ($n = 20$) (United Nations 2018), THF-F ($n = 14$) (United Nations 2018), carfentanil (United Nations 2018) ($n = 61$), methoxyacetylfentanyl ($n = 13$) (United Nations 2018), cyclopropylfentanyl ($n = 78$) (United Nations 2018). A total of 266 deaths were reported where there was confirmed exposure (toxicology analysis) to the substance under scrutiny; these were the cases analysed in detail. Out of 266 deaths, 233 deaths (90%) involved at least one other drug. Analogues of fentanyl were the cause of death or likely to have contributed to death in 161 out of 181 cases (89%). The Toxicology Significance Score was the highest (3) in 166 out of 176 cases (94%) with sufficient data. The deceased were mainly men (194/224, 87%) and the median age ranged from 29 to 43 years (depending on the substance).

Between 2014 and 2017, six countries (Croatia, Germany, Hungary, Poland, Sweden, and the United Kingdom) reported deaths involving synthetic cannabinoids with data included in the Risk Assessment of at least one of the four substances assessed. The synthetic cannabinoids involved were ADB-CHMINACA ($n = 13$) (United Nations 2018), AB-CHMINACA ($n = 31$) (United Nations 2018), CUMYL-4CN-BINACA ($n = 11$) (United Nations 2018), 5F-MDMB-PINACA ($n = 28$) (United Nations 2018). A total of 83 deaths were reported and in 67 of these, other drugs were also found (81%). A synthetic cannabinoid was the cause of death or was likely to have contributed to death in 46 out of 76 deaths with this information (57%). The Toxicology Significance Score (TSS) was the highest (3) in 60 out of 77 (78%) with sufficient data. The deceased were mainly men (64/72, 89%) and the median age ranged from 28 to 40 years.

4. Discussion

NPS were involved in more than 2300 DRD reported in Europe between 2016 and 2017. In these two years, NPS were identified in around one in seven DRD in Europe and accounted for a rate of 2.4 deaths per million inhabitants per year (3.6 deaths per 100,000 inhabitants aged 15-64 per year). Moreover, there was a significant increase in NPS-DRD between 2016 and 2017, especially regarding DRD involving novel benzodiazepines, novel opioids, and synthetic cannabinoids. However, one of the striking findings of our study is that most NPS-DRD deaths are concentrated in two countries (the United Kingdom –mainly Scotland – and Turkey) and related to very few substances. Nine out of ten NPS-DRD involved males, a higher proportion compared to all DRD in Europe (United Nations 2019, United Nations 2019). Despite scarce data on age, the deceased appear to be younger compared to all DRD in Europe. Polydrug intoxication is the norm and, in the vast majority of NPS-DRD cases, other drugs were found within toxicology, notably opioids in the case of Etizolam. When the cause of death could be studied (according to the TSS), within the very selected and focused context of risk assessment procedures, in 94% of DRD involving novel opioids and in 78% of DRD involving synthetic cannabinoids, the NPS appeared to be either the cause or a relevant contributor to the cause of death, although

Table 3
Number of DRD involving at least one NPS per molecules (at least 2 deaths registered).

Molecules reported in > 1 death	2016 (number of related deaths)	2017 (number of related deaths)
Novel opiates	U-47700 (13) Carfentanyl (5) Carfentanyl. acrylfentanyl or furanylfentanyl in Estonia (24)	U-47700 (10) Ocfentanil (3) Carfentanyl (35)
NPS-BZD	Etizolam (225)	Etizolam (301)
Other	Ketamine (8) GHB (25)	GHB (19) Ketamine (2)
Synthetic cannabinoids	AB-Chiminaca (2) ABD-Fubinaca (2)	5F-ADB or 5-ABD-MDMB-PINACA (2)
Novel stimulants	Alpha PVP (6) 5-APBD (2-Aminopropyl-benzofuran) (2) 4MMC (4-methylmethcathinone) or Mephedrone (18) 4-FA (4-fluoroamphetamine) ((2) Pentedrone (3) Ethyl-hexedrone (5)	N-ethylpentylone (2) Alpha PVP (15) 4MMC (4-methylmethcathinone) or Mephedrone (2) 3-MMC (3-methylmethcathinone) (2) Ethyl-hexedrone (6)

Table 4
Changes between 2016 and 2017. Percentages and OR (and 95% CI), by totals, by groups of substances and by countries.

	Net increase deaths (2016/2017, number of individuals)	Increase (number of deaths %) (#)	OR(##)
For Europe as a whole (22 countries with data in both years -2016 and 2017-, from EU 28 countries plus Turkey and Norway)			
DRD-NPS total	307	30%	OR 1.33, CI95% 1.23-1.45, z-statistic 6837, $p < 0.0001$
synthetic cannabinoids	200	48.5%	OR 1.49 CI95% 1.31-1.68, z-statistic 6013, $p < 0.0001$
novel benzodiazepines	56	16.4%	OR 1.20 CI95% 1.03-1.41, z-statistic 2295, $p < 0.0217$
novel opioids	74	59.7%	OR 1.66 CI95% 1.32-2.08, z-statistic 4373, $p < 0.0001$
For individual countries included in the study			
Austria	+8	266.7%	OR 3.64, CI95% 1.02-13.05, z-statistic 1.984, p=0.0472
Belgium	+5	100%	n.s.
Estonia	+2	8.3%	n.s.
Hungary	+1	7.7%	n.s.
Sweden	+35	38%	OR 1.37 CI95% 1.04-1.79, z-statistic 2.272, p=0.0231
Turkey	+188	49.9%	OR 1.47 CI95% 1.29-1.68, z-statistic 5.836, $p < 0.0001$
UK	+89	24.3%	OR 1.23 CI95% 1.07-1.41, z-statistic 2.963, p=0.0030
Lithuania	+7	N/A	N/A
Italy	+2	N/A	N/A
Czech Republic	+1	N/A	N/A
Germany	-1	- 1.3%	OR 0.99 (CI95% 0.7176-7.358, z-statistic 0.079, p=0.9370
Portugal	-1	N/A	N/A
Romania	-3	-75%	OR 0.25 CI95% 0.03-2.26, z-statistic 1.231, p=0.2185
Finland	0	0%	OR 1.00 CI95% 0.62-1.61, z-statistic 0.008, p=0.9939

#((DRD-NPS 2016) – (DRD-NPS 2017)/ (DRD-NPS 2016))*100.
Computation described in the text.
(N/A = Not applicable due to lack of NPS-DRD data in 2016).

it cannot be concluded that this high proportion apply to all NPS-DRD reported from the population as a whole.

Compared to general mortality (10,002 per million inhabitants across the EU-28 in 2016), general mortality in people under the age of 75 (3331 per million inhabitants across the EU-28 in 2016), and DRD mortality overall (23 per million inhabitants aged 15-64) in Europe, NPS-DRD are a rare phenomenon (46, United Nations 2019). However, victims of DRD are a comparatively young population (people in their 30s, 40s and 50s) and in the case of NPS-DRD the victims are younger than DRD overall, representing a substantial amount of years of life lost. Moreover, the mortality rate of NPS-DRD expressed for the general population appears low because this denominator dilutes the population at risk (Millar et al., 2017) (i.e. those who use NPS). If estimates of people who use NPS were available, this denominator would give a much better account of the mortality risk and excess risk of deaths associated with the use of NPS.

Besides fatal cases, the impact of acute drug toxicity can also be assessed by monitoring acute drug toxicity presentations to hospital emergency departments. The Euro-DEN Plus network, initially composed of sixteen sentinel centres in ten European countries found that 5.6% of

acute drug toxicity presentations involved NPS (2013-2014). By the end of 2018, there were 31 sentinel sites in 21 countries. While NPS were seen in 9 % of all presentations over the 4 years (2014-2017), they were identified in 4% of the presentations in 2018 (European Monitoring Centre for Drugs, 2020).There was a significant geographical variation in the involvement of NPS in presentations, and the predominant type of NPS changed from cathinones in 2014-15 to synthetic cannabinoids in 2016-17 (Euro-DEN Plus Network, 2020). Overall, during the first 12 months of data collection, 27 fatal outcomes were identified, 3 of which were related to NPS (Dines et al., 2015).

One of the main findings of our study was that cases were concentrated in two countries and related to two types of substances. The UK and Turkey reported three quarters (75.1%) of the total number of NPS-DRD between 2016 and 2017. This figure only takes into account information available in *Drug-related harms and harm reduction workbooks* to avoid potential overlapping if the Risk Assessment Report were also included. Etizolam cases (mostly in Scotland, UK) represented almost a third (30%) of NPS-DRD in Europe and synthetic cannabinoid cases in Turkey contributed 45% to Europe's NPS-DRD in 2016 and 2017.

Compared to deaths related to synthetic cannabinoids and etizolam, deaths involving other types of NPS (e.g. cathinones, novel opioids or others) were less commonly reported. The impact of this situation can be assessed; in 2017, there were 381 (5.2%) NPS-DRD deaths, out of 7362 DRD with toxicology, with an NPS different from the two groups described. The equivalent proportion for 2016 would be 4%.The European situation contrasts with the situation in other parts of the world such as North America, which is largely impacted by deaths associated with novel opioids, such as fentanyl and its derivatives (NIDA).

In our study, there was no information about the specific mechanism of death among the numerous deaths by synthetic cannabinoids reported in Turkey, but fatal acute poisoning linked to synthetic cannabinoids is well documented. Synthetic cannabinoids cause death by several disorders: delirium, psychosis, self-harm, trauma or accidents, myocardial infarction, ischemic stroke, acute kidney injury, seizures (Tait et al., 2016, Labay et al., 2016). Outside Europe, mortality due to cutting-agents (e.g. haemorrhage due to anti-coagulant) has also been described (Kelkar et al., 2018). There is information that supports the existence of widespread use of, and public concern about, synthetic cannabinoids in Turkey since the beginning of the 2010s. Hospital emergency data indicates frequent acute drug toxicity presentations in the country due to synthetic cannabinoids. The majority (89.7%) of patients admitted to emergency care for drugs in an Izmir hospital had used one or more synthetic cannabinoids (Caliskan et al., 2018).

Regarding etizolam, the substance is involved in a high number of overdose deaths (in almost all cases with the presence of opioids, and often with other substances) in Scotland (United Nations 2019). Regarding pharmacological potency, on the one hand, in medical practice the usual dosage is one fifth-tenth of diazepam indicating that on a weight basis, it is clinically ten times more active (United Nations 2019, Fracasso et al., 1991, Nielsen and McAuley, 2020). However, the potential adverse effects that lead to death are similar to those reported for diazepam or other benzodiazepines, especially if they are combined with other sedative drugs (Park et al., 2015): sedation and loss of consciousness (and occasionally bronchoaspiration and respiratory failure) (United Nations 2019). In addition, etizolam is typically sold as manufactured "street valium" (Lowther and Brocklehurst, 2019). This it is more difficult to self-administer the exact dose, due to confusion about the main active compound and unknown concentration of etizolam. Finally, it was reported that the street price of etizolam tablets was notably cheaper than various commercial benzodiazepines, and ingestion of several tablets on the same occasion was common (Doward, 2019, United Nations 2017). Although the reasons for high levels of availability and deaths related to etizolam in a specific jurisdiction are still to be fully understood, the high prevalence of opioid use, the aging population of people using drugs, poverty, untreated mental health issues and problems of alcohol use may together contribute to the alarmingly high rates of DRD involving this NPS. Scotland, had the highest mortality rate in 2018, with 295 deaths per million adult population aged 15-64, almost 4 times the UK average, and more than 13 times the European average (European Monitoring Centre for Drugs and Drug Addiction, 2020). In Scotland (2017), 36% of DRD involved a novel benzodiazepine – mainly etizolam (National Records of Scotland, 2018).

After synthetic cannabinoids and etizolam, novel opioids, primarily related to fentanyl analogues, are the NPS involved in most deaths. Estonia showed high mortality related to fentanyl-analogues until 2017. Since 2005, the problem has been in the public health domain (e.g. 3-methylfentanyl) and has been defined as an 'endemic' problem (Ojanperä et al., 2008, Mounteney et al., 2015). Fentanyl analogues are used as a recreational substance and are mixed with other drugs worldwide (Mounteney et al., 2015, Minutillo et al., 2019). Unknown consumption as an drug mixed with others is even riskier due to higher potency compared with heroin (Ciccarone et al., 2017). According to the National Crime Agency (UK), fentanyl has been extensively identified as an additional substance in heroin specimens (National Crime Agency, 2017). Novel opioids, and in particular fentanyl analogues, deserve particular attention due to their high potency, which poses a high risk of fatal overdose to users.

4.1. Limitations and strengths

A first limitation is the likely existence of some under-identification and underreporting of deaths related to NPS (either as an underlying cause of death or as a contributory factor). There are also variations in the forensic laboratory practices across Europe, and cases might be missed in some countries (EMCDDA, 2019). This is a common limitation for overall DRD comparison across Europe and is not exclusive to NPS, although it is likely to be more of a problem for NPS, in particular in some countries. For instance, in eight of the included countries participating in the study, reported no cases neither in 2016 nor 2017 leaving open the possibility that there was underreporting.

The majority of the over 800 NPS monitored by the EWS are not routinely screened for in laboratories conducting toxicology on DRD. In addition, there are no pharmacological studies for many of the substances monitored and therefore the metabolites may be unknown; and for some highly potent substances, highly-sensitive techniques as well as expensive reference standards may be required for their detection. However, although in strict sense it is unknown what proportion of the over 800 NPS monitored by the EMCDDA is simultaneously available in the market, since 2015 only approximately 400 previously reported NPS are detected in a sample and reported to the EWS each year in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2020). Furthermore, studies based on wastewater analysis in 24 cities of 16 European countries suggest that the amount of NPS actually present in the market at a detectable level is relatively limited (United Nations 2020, Salgueiro-Gonzalez et al., 2019).

The EMCDDA is currently monitoring 30 new benzodiazepines — 21 of which were first detected in Europe since 2015 (European Monitoring Centre for Drugs, 2020). However, due to the absence of risk assessments on novel benzodiazepines, it has not been possible to use this type of information in the study.

Despite these limitations, several European countries show sufficient capacity to identify NPS-DRD even at low concentrations, which for potent substances can sometimes be at a nanogram per millilitre level or even lower, and identify different substances in the same sample, as illustrated in the Risk Assessments and the ongoing reporting through the EWS and the Drug-related harms and harm reduction Workbooks. For these reasons, although some under-detection and under-reporting to the EMCDDA is likely, identification capacity seems reasonable in many countries, and a relevant number of countries can detect NPS-DRD with a broad range of different NPS. Moreover, the triangulation of three different reporting systems (EWS, standardized routine DRD reporting and the structured Workbooks) indicates that a substantial or biased under-

reporting is unlikely. In 2017, data from a few countries were partial or non-existent at the time of extracting information for this study (Autumn 2019). This possibly caused some underestimation of NPS-DRD for that year.

At the time of conducting this research, fewer countries (24) had reported DRD cases in 2017 than in 2016 (27). However, the countries without data in 2017 had reported few NPS-DRD cases for 2016. The total number of NPS-DRD deaths for 2017 could be modestly higher than that reported here, and the reported increase is conservative. On the other hand, the high proportion of DRD with a mention of any NPS in 2017 (18.1%) possibly represents some overestimation. The OR were computed using comparable populations for 2016 and 2017, including only countries reporting on both years.

The information presented in this study corresponds to the years 2016 and 2017, which might be considered somewhat outdated at the moment of publication. In one hand the complexity of the data transmission from national sources lead that at the moment of data collection (end of 2019) only 2016 and 2017 could be considered reasonably completed. In addition, the situation during 2020 with COVID-19 pandemic delayed the process of drafting the paper. Even so the data presented here it should be considered as first overview, and it would be important to continue further work in this quickly changing phenomena. For instance, there is already information that the number of cases in one of the countries reporting most deaths related to NPS have registered substantial decreases. Further and updated research in this field is guaranteed.

Despite these limitations, our study was the first population-based epidemiological analysis of NPS-DRD across Europe. In addition, we retrieved information from standardized and well-established systems that enables the current situation to be better understood, and gaps to be identified (possible underestimation, unestablished causality, sociodemographic characteristics, and trends) (Tables 3 and 4).

5. Conclusions

Overall, in 2016-2017, one out of seven DRDs across Europe involved at least one NPS, with some likely underreporting. However, this finding should be interpreted with caution, as the distribution of NPS-DRD is very heterogeneous, with two countries (Turkey and the United Kingdom) concentrating three quarters of these deaths, which were related to two types of substances: novel benzodiazepines and synthetic cannabinoids, together accounting for nearly 70% of all European cases. The situation in each of these two countries should be studied further, in order to develop effective interventions. Additional research should focus on the pharmacology of NPS, in a better understanding of the forensic and toxicology capacity, in reporting practices across Europe and in the triangulation with other sources and methodologies (e.g. hospital emergencies, wastewater analysis, seizures or others). Future studies should also focus on the patterns and circumstances of use and other sociodemographic characteristics of users, in order to identify at-risk populations and to guide responses. Identifying the magnitude of the problem and the country-specific situation will aid to formulate targeted policy and health interventions (harm-reduction, guidelines for practitioners in emergency services).

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Author Contribution

HLP and JV designed the study. HLP and JV wrote the first draft of the manuscript. All authors contributed to the editing and final review of the manuscript. All authors have approved the final article.

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.

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Supplementary materials

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