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Research Paper

Substances from unregulated drug markets – A retrospective data analysis of customer-provided samples from a decade of drug checking service in Zurich (Switzerland)

Raphael Magnolini[a,*], Martina Schneider[b], Dominique Schori[b], Daniel Trachsel[c], Philip Bruggmann[a,d]

[a] Arud Centre for Addiction Medicine, Zürich, Switzerland
[b] Drug Information Centre 'DIZ', City of Zurich, Department of Social Welfare, Zurich, Switzerland
[c] ReseaChem GmbH, Burgdorf, Switzerland
[d] Institute of Primary Care, University of Zurich and University Hospital Zurich, Zurich, Switzerland

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ABSTRACT

Background: Drug checking services (DCS) are harm reduction interventions for people who consume illicit substances. Unregulated drug markets lead to samples with unexpected and variable contents. A retrospective data analysis of Zurich's DCS was performed to determine the nature of these samples.

Methods: This study aims to investigate the qualitative and quantitative properties of 16,815 customer-provided psychoactive drug samples analyzed chemically through the DCS in Zurich from 1st January 2011 to 31st December 2021. The main analytical method utilized for characterizing these substances was high-performance liquid chromatography and gas chromatography–mass spectrometry. Data sets are summarized using descriptive statistics.

Results: There was a 2.5-fold increase in the number of tested samples over the past decade. An overall proportion of 57.9% (weighted mean) of samples within our database demonstrates unexpected analytical findings and additional low sample contents during the observation period. Substantial differences in quality and quantity between substance groups were detected and an increase of sample quality and content over time was demonstrated.

Conclusions: Chemical analysis reveals that over half of substances acquired from unregulated drug markets analyzed through DCS in Zurich are with low qualitative and quantitative properties, which may expose users to risks. Based on longitudinal analyses over a decade, this study contributes to the body of evidence that DCS may potentially manipulate unregulated drug markets towards providing better quality substances, as well as may stabilize these markets over time. The necessity for drug policy changes to make this service accessible in further settings was highlighted, as DCS still often take place in legal grey zones.

Background

Drug checking is a harm reduction intervention that is intended for people who consume drugs that were acquired from unregulated drug markets. They submit samples for chemical analysis and receive feedback on the composition of their samples. Commonly this approach is embedded in a wider harm reduction approach that includes counselling services for this often hard to reach group of users (Maghsoudi et al., 2022). The actual content of substance samples acquired from unregulated drug markets often remains unknown which can leave users at an unpredictable risk. The substances and/or adulterants can potentially lead to extensive negative health outcomes and are considered a sub-

Abbreviations: DCS, Drug checking services; DIZ, Drug information centre; HPLC, high-performance liquid chromatography; DAD, a diode-array detector; GC-MS, gas chromatography–mass spectrometry; LC-MS, liquid chromatography-mass spectrometry; NMR, nuclear magnetic resonance spectroscopy; NPS, new psychoactive substances; EMCDDA, European Monitoring Centre for Drugs and Drug Addiction; AI, Active ingredient; 2C-B, 4-Bromo-2,5-dimethoxyphenethylamine; mCPP, 1-(3-Chlorophenyl)piperazine; DMT, *N,N*-Dimethyltryptamine; GHB, γ-Hydroxybutyric acid; LSD, Lysergic acid diethylamide; Methylone, 2-Methylamino-1-(3,4-methylenedioxyphenyl)propan-1-one; Mephedrone, 4-MeMC, 4-Methylmethcathinone; Metaphedrone, 3-MMC, 3-MeMC, 3-Methylmethcathinone; PMMA, 4-MMA, Paramethoxymethamphetamine; PMA, 4-MA, Paramethoxyamphetamine; DOB, 4-bromo-2,5-dimethoxyamphetamine; DOI, 2,5-dimethoxy-4-iodoamphetamine; DOM, 2,5-dimethoxy-4-methylamphetamine; MDMA, 3,4-methylenedioxymethamphetamine.

* Corresponding author.
E-mail address: raphael.magnolini@yahoo.com (R. Magnolini).

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stantial individual and public health threat ("Hedegaard et al., 2020; Nieschlag & Vorona, 2015).

Since their formal introduction in the 1990s, drug checking services (DCS) are now conducted in a growing number of countries, predominantly across Europe ("Barratt et al., 2018; Winstock et al., 2001). In the recent past, DCS have emerged as a potential harm reduction intervention with expansions in North America and worldwide (Green et al., 2020; Maghsoudi et al., 2020; Measham, 2020; Scarfone et al., 2022; Sherman et al., 2019; Tupper et al., 2018), particularly in response to the emerging global opioid crisis and increasing opioid-related overdoses (Barocas et al., 2022; "Hedegaard et al., 2020; Lewer et al., 2022).

The peer-reviewed research evidence related to drug checking is limited and primarily based on the long-standing history of drug checking within electronic dance and festival settings (Barratt et al., 2018; Ivers et al., 2021; McCrae et al., 2019; Measham, 2020; Measham & Turnbull, 2021; Measham, 2019; Mema et al., 2018; Murphy et al., 2021; Palamar et al., 2021; Sande & Šabić, 2018; Valente et al., 2019) and more recently, in light of the opioid crisis, people who use opioids (Dolan et al., 2021; Glick et al., 2019; Karamouzian et al., 2018; Laing et al., 2018; Mema et al., 2018; Palamar et al., 2020; Ti et al., 2020; Tupper et al., 2018; Wallace et al., 2021; Wallace et al., 2020). More peer-reviewed research is needed with a focus on the general population and the overall effectiveness of this harm reduction intervention. Articles providing chemical analyses' results of sample through DCS demonstrate that unexpected analytical findings among those substances is common, with particularly high proportions of adulteration products among synthetic opioids (Brunt & Niesink, 2011; Gerace et al., 2019; Gozdzialski et al., 2021; Oomen et al., 2022; Tobias et al., 2021; Tupper et al., 2018).

DCS in Switzerland have existed since end of the 1990s and they are central elements in the Swiss drug policy that aims to reduce drug use and its negative consequences for users and society. In Zurich (Switzerland), the Drug Information Centre (DIZ), an information and counseling center that offers DCS, was established in 2006. Zurich demonstrates substantial use of substances, such as cocaine, amphetamine, MDMA and methamphetamine, determined by international wastewater analyses (Wastewater analysis and drugs, 2021).

Regarding the growing availability and research interest of DCS worldwide, a retrospective database analysis on chemically analyzed substance samples from unregulated drug markets provided by service-users through Zurich's DCS was performed. To our knowledge, this is one of the largest recent retrospective data analyses within the peer-reviewed published literature of DCS, analyzing these substances qualitatively and quantitatively over a decade.

Methods and materials

Study aim

The goal of this study is to investigate the nature of illicit substances analyzed through Zurich's DCS between 2011 and the end of 2021. It aims to assess the following parameters: i) the change in test volume over time and type of tested substances, ii) the quality and quantitative content of tested substance samples (cross-sectional data), and iii) the change in quality and quantitative content for a sub-group of tested substances over time (longitudinal data).

Study setting

The DCS Zurich "DIZ" was established in 2006 as the first specialized agency in Switzerland to offer drug checking in addition to drug information and counselling. The "DIZ" is a public service of the department of Social Welfare of the City of Zurich.

Study design

A retrospective database analysis of user-provided substances through the stationary DCS and analyzed by its collaborating Laboratory (ReseaChem GmbH) from 1st January 2011 to 31st December 2021 was conducted. The year 2011 was chosen as all methodological and analytical processes were then validated after its establishment in 2006.

Study procedures

The samples relevant to this study were received anonymously, directly from service-users and were analyzed at ReseaChem GmbH (Switzerland), the collaborating laboratory. One substance sample per person was eligible for testing. In order to classify these substances, the classification system under the US federal Controlled Substances Act (CSA) of 1970 (21 U.S.C §812(b)) was used. It aims to provide a comprehensive and uniform structure for classifying substances of abuse. Under the CSA, controlled substances are divided into five "schedules", according to their potential for abuse, their use in medicine and their potential for addiction (supplementary Table 1). Supplementary Table 1 includes examples of analyzed substances that are provided by Zurich's DCS.

Qualitatively, chemically analyzed samples were further classified into the three groups, i.e., "expected analytical result" and "unexpected analytical result" based on the declared content by service users, as well as "unknown" if the content was not declared. "Unexpected analytical results" were further sub-categorized into "inert", "substituted" and "adulterated". All respective definitions are provided in Table 1.

The definition of adulterated substances was adapted from Cole and colleagues (Cole et al., 2011) as pharmacologically active ingredients (AI) that are added to enhance or mimic the effects of the expected substance, and contaminants that are results of poor manufacturing techniques, e.g., cross-contamination from poorly cleaned scales.

Quantitatively, chemically analyzed samples were further classified into the two groups, i.e., "high" and "low" sample content. Further additional analytical quantitative categories were defined. All respective definitions are provided in Table 2. Quantitative categorization was based on internal benchmarks used.

A longitudinal subgroup analysis was performed for cocaine, MDMA and amphetamine. These chemically analyzed substances were observed over time and grouped by year from 2011 to 2021.

Sample preparation and chemical analysis

The products existed in different galenic forms. Different chemical analysis methods were applied. The chemical analysis methods included a qualitative analysis as well as a quantitative analysis and were conducted by high-performance liquid chromatography (HPLC) with a diode-array detector (DAD), gas chromatography–mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), and nuclear magnetic resonance spectroscopy (NMR). The general analysis protocol and indication for the use of each method is described in detail in supplementary file 1.

Data collection and management

Sample data was documented in separate electronic data sheets for each drug testing until 2020. Since beginning of 2021, the data has been recorded directly into a shared database, allowing an up-to-date and secure export of data at any time. Data from acquired samples were entered into the database directly by the social workers during each

Table 1
Classification of qualitative results.

Classification	Criteria and terminology
Expected analytical result	Qualitative formulation detected fully matches the one declared
Unexpected analytical result	Qualitative formulation detected does not match the one declared Subclassification: - *Inert*: refers to no AI present - *Substituted*: refers to other AI or synthetic impurities present instead of the one declared - *Adulterated*: refers to other AI or synthetic impurities present in addition the one declared
Unknown	No information available regarding the identity of AI was declared

AI= active ingredient

Table 2
Classification of quantitative results.

Classification	Criteria and terminology
High sample content	Levels of AI detected are above the defined threshold*
Low sample content	Levels of AI detected are below the defined threshold*
Quantitative categories	Levels of AI detected are between a defined range Subclassification: - Very low levels of AI: >0-20 % (powders); >0-50mg (MDMA pills) - Low levels of AI: >20-40 % (powders); >50-100mg (MDMA pills) - Moderate levels of AI: >40-60 % (powders); >100-150mg (MDMA pills) - High levels of AI : >60-80 % (powders); >150-200mg (MDMA pills) - Very high levels of AI : >80-100 % (powders); >200mg (MDMA pills)

AI= active ingredient
* The threshold for low sample content was defined as substances that reached a content of <60% for powders, crystals or liquid galenic formulations. Pills containing MDMA contents below 120mg (Green et al., 2003), 2C-x pills contents below 10mg, and LSD blotter below 100μg were considered low sample content.

consultation. Service users declared the content of the acquired substance. Results from chemical analyses were entered into an electronic data form that was automatically generated from these entries. Results of the composition and content of these substances were provided to the users individually, as well as uploaded on a homepage provided by the department of social welfare of Zurich, thus were accessible to the public (https://en.saferparty.ch). Data extraction and data cleaning was done quarterly for internal data reports for a subset of substances. The data extraction for this study was done in January 2022 after all data collection was finalized and was stored in a secured cloud system. Only authorized personnel from the department of social welfare were authorized access to the database.

Sample size

A sample number “n” of a substance group with a minimal sample size (n ≥30) over the complete observation period of 2011 to 2021 was considered for a qualitative and quantitative statistical analysis ("Hogg and Tanis, 1997). Sample numbers of substances with a sample size (n <30) were excluded.

Statistical methods

Data sets were summarized using descriptive statistics. To assess differences in proportions, the “N-1” chi-squared test was used (Campbell, 2007; Richardson, 2011). Confidence intervals were calculated ("Altman et al., 2000). To assess differences in the mean content of two substances, a two-sided t-test was used. All probability values were reported as two-tailed probability values, and ≤ 0.05 was taken as the level of significance ("Altman, 1991). MedCalc statistical software was used for data analyses ("MedCalc Software Ltd., 2022). For trend analyses a simple regression model using R-squared was used for longitudinal data. The strength of the relationship based on R-squared was defined based on "Moore et al. (2013) as <0.3 none, 0.3-0.5 weak, 0.5-0.7 moderate and >0.7 strong.

Results

Declared samples

The flow diagram of substances analyzed at Zurich’s DCS between 1st January 2011 and 31st December 2021 is shown in Fig. 1. The data from 16,815 samples was extracted. After removing mixed samples (n=21), incomplete datasets (i.e., cannabinoids that could not be quantitatively analyzed within the scope of the project, n=222) and samples with problematic declarations or missing data (n= 174), a total n= 16,398 monosamples were included in the statistical analysis.

As demonstrated in Table 3, three substances accounting for the biggest proportion (approx. 80 %) of analyzed samples, consisting of cocaine (n=7,184, 43,8%), MDMA (n=2,850, 17.4%) and amphetamine (n=2,806, 17.1%). All other tested samples made up less than 10% of all declared substances, including LSD, heroin, ketamine, 2C-x derivates, and methamphetamine. A total of n=608 (4%) samples were declared as “unknown” by service users. For “other” substances (n=373, 2.3%) with a test volume of less than 1% of the total of declared samples, five substance groups made up the majority and approximately 70% of tested samples, which included DMT, mescaline, mephedrone, benzodiazepines and psilocybin/psilocin.

The overall test capacity at DCS Zurich had a 2.51-fold increase within a decade, from n=787 tested samples in 2011 to n=1,972 samples in 2021. The test capacity has steadily increased over time, with one slight decrease in 2020 as result of the COVID-19 pandemic and its associated limitations of public life as demonstrated in Fig. 2.

Tested samples for amphetamine and heroin have decreased, comparing 2021 to 2011, whereas tested samples for MDMA, cocaine, ketamine, methamphetamine, LSD, and 2C-x derivates have increased (Fig. 2). There were steady increases of tested samples over the observation period for declared cocaine, LSD, and ketamine, whereas intermittent courses over time were seen for declared MDMA, amphetamine, heroin, and methamphetamine (Fig. 2). For ’other’ substance groups, the most important increase in tested samples were documented for psilo-

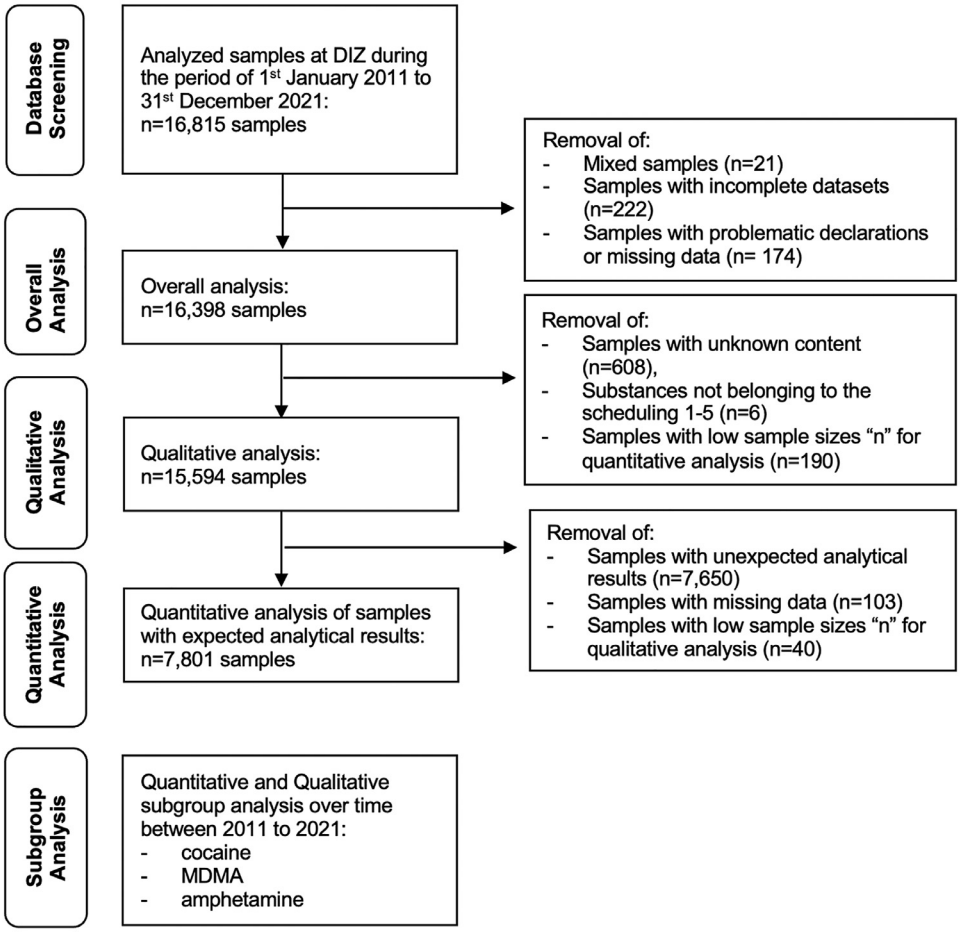

Fig. 1. Workflow diagram.

Table 3
Cross-sectional analysis of n=16,398 samples declared at drug checking Zurich during the observation period of 2011 to 2021.

Substance	Overall *N* included	Proportion of total *N* (%)	*N* included in 2011	*N* included in 2021
Cocaine	7,184	43.81	265	805
MDMA	2,850	17.38	203	353
Amphetamine	2,806	17.11	202	192
LSD	1,340	8.17	34	235
Heroin	408	2.49	20	16
Ketamine	360	2.20	7	94
2C-x derivates	261	1.59	8	44
Methamphetamine	208	1.27	3	39
Others	373	2.27	11	120
Unknown	608	3.71	34	74
Total *N*	16,398	100.00	787	1,972

cybin/psilocin, mephedrone, DMT and mescaline, as well as benzodiazepines.

Results of the chemical sample analysis

Qualitative analysis

Substance groups were categorized according to scheduling under the controlled substances act. Overall, n=15,594 eligible chemically analyzed samples were included after removal of some samples according to the reasons mentioned in Fig. 1. Among the included samples, 5,036 (32.3%), 10,198 (65.4%) and 360 (2.31%) samples belonged to schedule 1, 2 and 3, respectively. No Schedule 4 and 5 substances were included for quantitative and qualitative statistical analyses. Across all chemically analyzed samples, unexpected analytical results were detected in 7,650 samples (weighted mean: 49.1% (SD= 22.5)). Among these samples, the vast majority were adulterated (93.2%), and, in the minority of samples, substances were substituted, or no active ingredient could be detected at all. Major differences can be seen among schedules, as it appears that in schedule 2 substances most unexpected analytical results were detected (Table 4).

High variation between individual substance groups were observed. The highest amount of unexpected analytical results detected by far were in samples declared as heroin (99.3 %). Other psychoactive substance groups with high proportions of unexpected analytical results detected were amphetamine, DMT and cocaine, whereas low proportions were detected in ketamine, methamphetamine and MDMA as demonstrated in Fig. 3. Interestingly, adulteration accounts for the largest proportion of unexpected analytical results for most individual substances, except mephedrone.

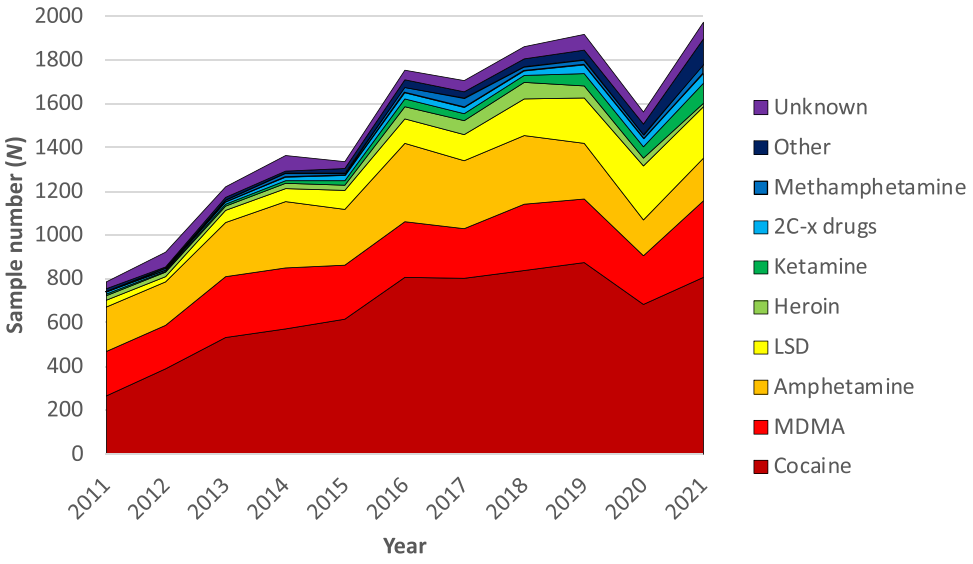

Fig. 2. Longitudinal analysis of n=16,398 samples declared at drug checking Zurich during the observation period of 2011 to 2021.

Table 4
Qualitative analysis of samples declared at drug checking Zurich during the observation period of 2011 to 2021.

S	Number included		Unexpected analytical results		Adulteration		Substitution		Inert	
	Total N=		*N=*	*Mean (SD)*	*N=*	*Mean (SD)*	*N=*	*Mean (SD)*	*N=*	*Mean (SD)*
1	5,036	100%	1,555	30.9% (25.7)	1,241	24.6% (24.8)	221	4.39% (5.85)	93	1.85% (1.61)
2	10,198	100%	6,048	59.3% (11.6)	5,860	57.5% (11.7)	149	1.46% (0.55)	39	0.38% (0.94)
3	360	100%	47	13.1% (0)	29	8.06% (0)	15	4.17% (0)	3	0.83% (0)
Total	15,594	100%	7,612	49.1% (22.5)	7130	45.7% (23.5)	385	2.47% (3.63)	135	0.87% (1.37)

SD= standard deviation
Qualitative analysis: overall number of tested substances and total number of further analyzed samples and the corresponding proportion and weighted mean including weighted standard deviation is given for the scheduling under the controlled substances act (Schedule (S) 1-3). For each schedule, the total number and proportion of samples found to be "unexpected analytical results", "adulterated" "substituted" and "inert" according to the definitions, are given.

Table 5
Quantitative and overall analysis of samples declared at drug checking Zurich during the observation period of 2011 to 2021.

S	Overall *N* included	*N* expected analytical results included	Proportion of expected analytical results with low sample content		Overall proportion of unexpected analytical results and additionally low sample content	
	N=	*N=*	*N=*	*Mean (SD)*	*N=*	*Mean (SD)*
1	5,036	3,380	1,056	31.2% (21.6)	2,611	51.3% (26.5)
2	10,198	4,122	307	7.45% (7.60)	6,355	62.3% (13.2)
3	360	299	9	3.01% (0)	56	15.6% (0)
Total	15,594	7,801	1,372	17.6% (19.4)	9,022	57.9% (20.2)

SD= standard deviation
Quantitative and overall analysis: the overall number of tested samples and total number of analyzed samples with expected analytical results, and the corresponding proportion and weighted mean and weighted standard deviation are given for the scheduling under the controlled substances act (Schedule (S) 1-3). For each schedule, the total number and proportion of samples found to be "low sample content" according to the definitions and "overall proportions", are given.

Among the n=15,594 samples that were chemically analyzed, a total of n=7,130 adulterated samples were detected, of which approximately 90% contained one or two additional active ingredient(s).

Quantitative analysis

A total of n=7,801 of samples with expected analytical findings were further evaluated for quantity. Overall, 1,372 samples (weighted mean= 17.6%, SD= 19.4) were found to be of low sample content. Combining both qualitative and quantitative chemical analyses, an overall weighted mean of 57.9% (SD= 20.2) of samples at DCS Zurich demonstrated unexpected analytical findings and were additionally of low sample content. This includes a small range of error due to missing data (n=103) and excluded samples due to low sample sizes (n=40) for the quantitative analysis (Table 5). Among samples with expected analytical findings, the measured levels of the declared active ingredient varied considerably between substance groups (Fig. 3), with some levels of active ingredient detected only in traces, others contents in very high amounts.

Low sample content was highest in Schedule 1 samples. Substances with the highest proportion of low sample content were LSD and mescaline, whereas low proportions of low sample contents accounted for methamphetamine, ketamine and cocaine as shown in Fig. 3.

An additional analysis comparing quantitative test results for unadulterated samples compared to adulterated samples demonstrated that mean contents of the declared active ingredient showed highly significant differences ($p < 0.0001$) for cocaine (22.9% (±0.40; 95% CI [22.1; 23.7])), MDMA pills/capsules (47.0mg (±4.31; 95% CI [38.6; 55.5])) and amphetamine (34.2% (±1.28; 95% CI [31.7; 36.7])).

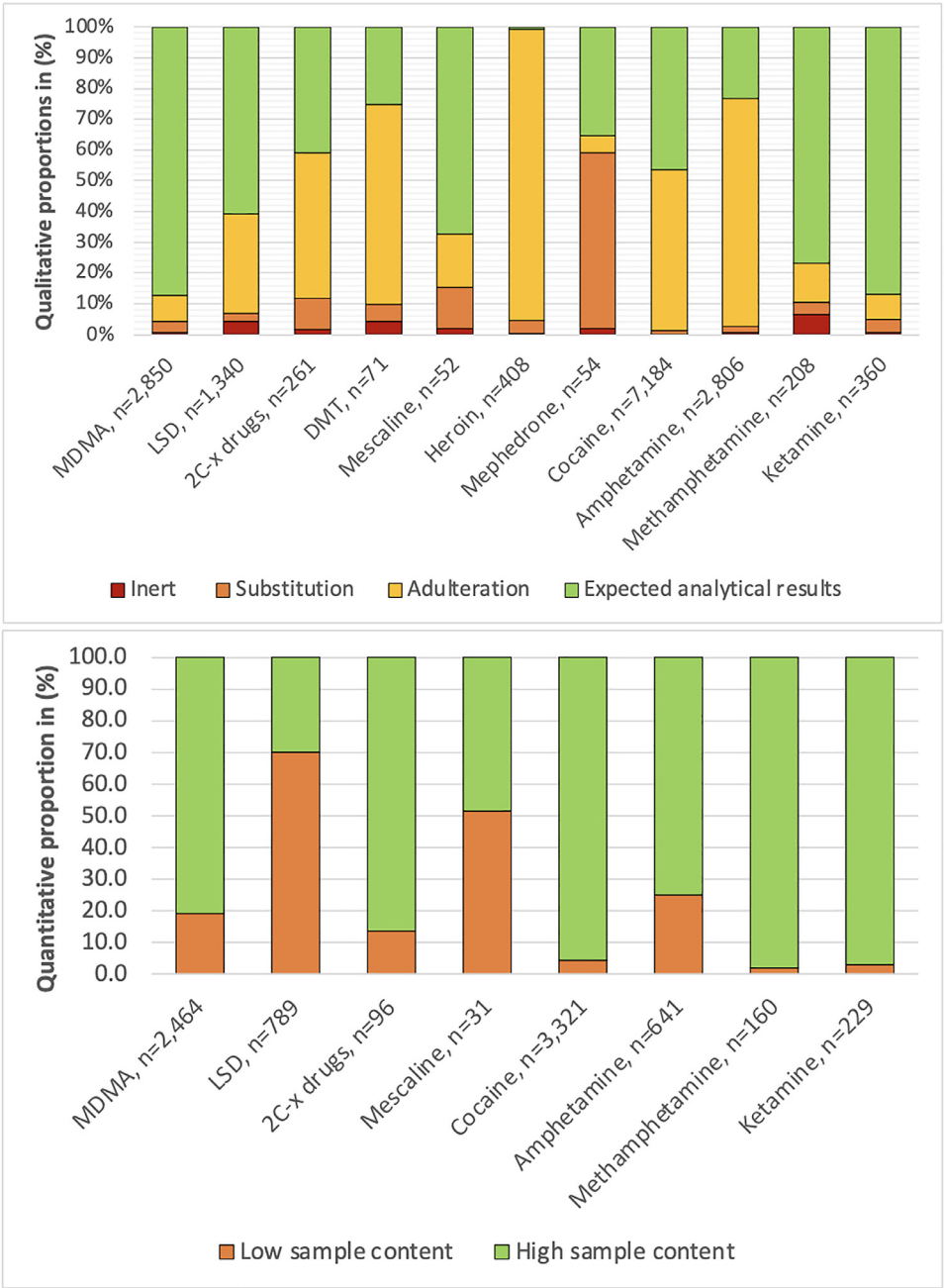

Fig. 3. Individual qualitative analysis results (n=15,594) and quantitative analysis results of samples with expected analytical results (n=7,801) of different substance groups received at drug checking Zurich, 2011 to 2021. Qualitative (above) analysis and quantitative analysis of expected analytical results (below) of included individual samples of different declared substances at drug checking Zurich during the observation period of 2011 to 2021 with their respective classifications and subclassifications.

Fig. 4 demonstrates examples of qualitative and quantitative analytical test results of declared substances at DCS Zurich that were acquired in 2021, illustrating different galenic forms that were analyzed (i.e., crystals, powders, plant-based, pills, blotters), as well as different unexpected analytical results (i.e., high sample content, adulteration, and substitution).

Subgroup analysis for cocaine, MDMA and amphetamine

The qualitative and quantitative development over time from 2011 to 2021 for cocaine powder, MDMA pills/capsules and amphetamine powder was evaluated. For interpretation of the quantitative analysis, all chemically analyzed results were included, irrespective of whether the chemical analytical findings were expected or unexpected. Overall, the qualitative analysis results demonstrate a significant difference in proportions of expected analytical results comparing 2021 to 2011, although differences could differ greatly between substance groups (Table 6). Furthermore, also highly significant, and substantial differences in proportions of samples with high sample contents, as well as mean contents of active ingredients, were observed comparing the respective years for the investigated substances (Table 6).

Over time, a steady increase of proportions of qualitative tested proportions can be observed for cocaine until 2017, thereafter the proportions remained fairly stable (Fig. 5). For MDMA and amphetamine, fluctuating trends were observed over time (supplementary Fig. 1). Furthermore, quantitative results for cocaine also demonstrated a steady increase until 2017 and remained stable thereafter (Fig. 5). For amphetamine and MDMA, similar trends can be observed (supplementary Fig. 2). Trend statistics for longitudinal data using R-squared demonstrate uptrends with strong effect sizes (>0.7) for quantitative analyses, including mean contents of active ingredients, as well as proportion of samples with high contents for all investigated substance groups over

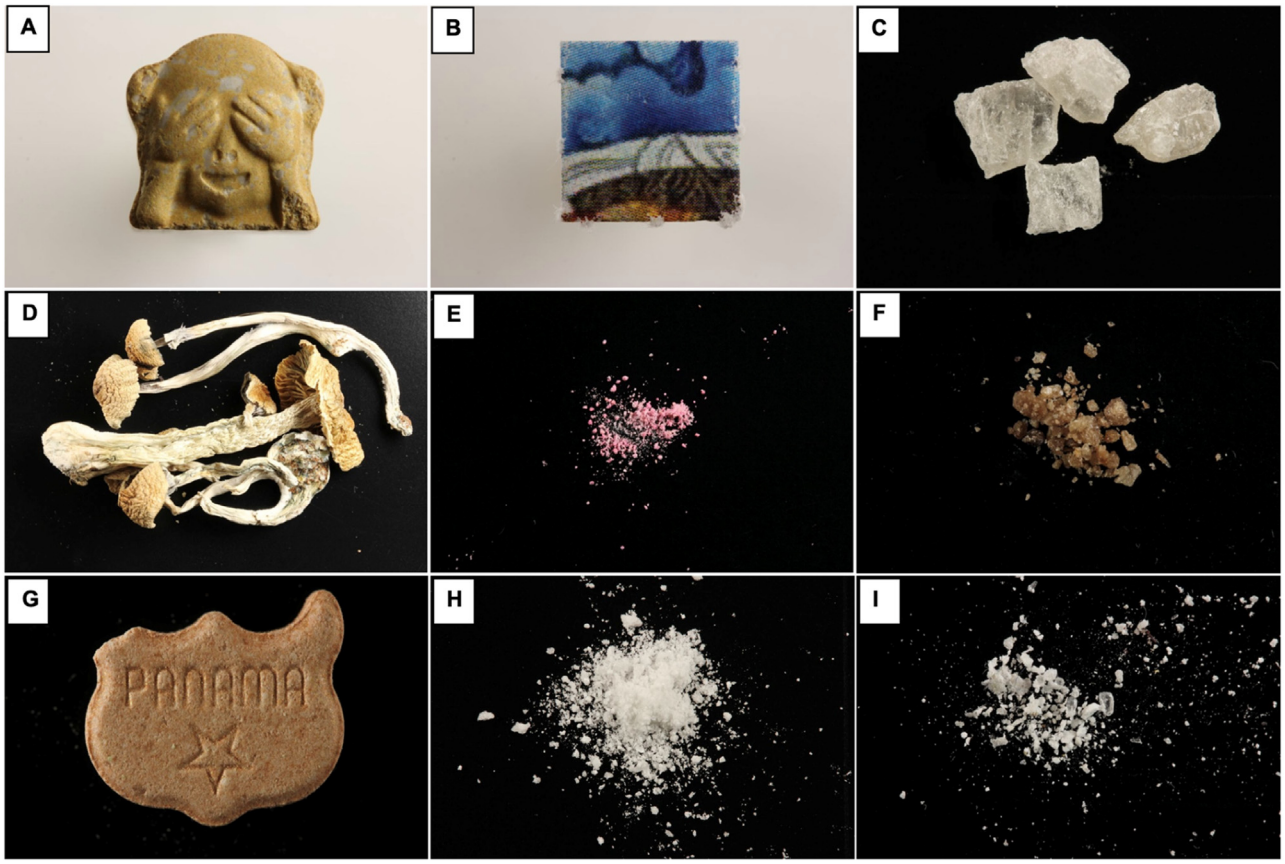

Fig. 4. Examples of qualitative and quantitative analyzed substance samples at drug checking Zurich in 2021.
Examples of analytical findings of declared vs. contained substances at drug checking Zurich in 2021: *Quantitative:* (A) pill with 'monkey no see' logo declared MDMA, contained high content MDMA (300.3mg); (B) blotter declared LSD, contained high content LSD (285.7µg); (C) crystals declared MDMA, contained high content MDMA (91.9%); (D) mushrooms declared psilocybin/psilocin, contained psilocybin (0.4%)/psilocin (0.37%); *Qualitative: Substitution* (E) pink powder declared 2C-B, contained MDMA, ketamine, acetylsalicylic acid, and salicylic acid; (F) brown crystals declared mephedrone, contained 4-CMC; *Adulteration* (G) pill with 'panama' logo declared MDMA, contained MDMA and 3-CMC; (H) white powder declared cocaine, contained cocaine and levamisole; (I) crystals declared cocaine, contained cocaine, heroin and ketamine.

time. Qualitative analyses demonstrate uptrends with strong, moderate, and weak effect sizes for cocaine, amphetamine, and MDMA, respectively.

Discussion

In this retrospective data analysis of substance samples analyzed through drug checking Zurich from 2011 to 2021, overall, 16,398 chemically analyzed samples were evaluated for statistical analysis, with 15,594 samples being analyzed solely qualitatively and 7,801 samples with expected analytical findings being additionally analyzed quantitatively. We demonstrate that substantial proportions of substances acquired from unregulated drug markets contain samples with unexpected and variable contents. The weighted mean for samples with unexpected analytical findings among the included samples was 49.1%. An additional proportion of 17.6% of samples demonstrated low sample contents, resulting in an overall proportion of 57.9% (weighted mean) of samples with unexpected findings and additional low sample contents within our database for the observation period. Major differences between substance groups were detected and this very wide range in proportions of unexpected and variable sample contents leaves users with unpredictable risks when consuming them. Besides the known side effects and adverse events of the declared substances, additional health risks may arise due to the use of adulterants. These substances can potentially lead to extensive unexpected negative health outcomes, which are substantial individual and public health threats ("Hedegaard et al., 2020).

Three traditional recreational substances accounted for the vast majority, and approximately 80% of all tested samples, namely cocaine, MDMA and amphetamine. Most samples with unexpected analytical findings were adulterated and contained various additional psychopharmacologically active compounds, but some of these samples have also been shown not to contain any active ingredient at all or were substituted by another active compound. Importantly, most of the adulterated samples contained one or two additional active ingredient(s) and/or synthetic impurities.

The term adulterant in this article is used to refer to active ingredients in addition to the declared active ingredient or presence of synthetic impurities. Although not all adulterants or substitutes are considered to be harmful (e.g., some by-products from the synthesis of compounds, caffeine, or paracetamol), the identification of potentially dangerous substances is of importance because these substances might be more toxic than the actual declared substance itself. Furthermore, large variations across quantitative results were observed within our study samples. The study included samples of nearly 100 % purity (e.g., powders) as well as extremely high levels of active ingredients (e.g., pills), which were neither diluted nor adulterated. As an example, in 2011 the highest content of MDMA per pill was at 165mg, whereas in 2021 extremely high contents of over 300mg per pill were detected. In contrast, other samples had such low levels of active ingredients in the tested sample that any pharmacological effect is doubtful. These large variations

Table 6
Comparison of qualitative and quantitative analytical test results for declared cocaine, MDMA and amphetamine at drug checking Zurich over time, 2011 to 2021.

Proportion (%) of samples with expected analytical content				
Comparison of samples from 2021 to 2011				**Linear regression from 2011 to 2021**
Substance	**Prop. in 2011 (%)**	**Prop. in 2021 (%)**	**Difference [95% CI]; X^2; p value**	**R^2; Pr > F**
Cocaine	8.68% (23/265)	66.5% (535/805)	57.8% [52.6%; 62.0%]; 266.484; p < 0.0001	0.893: 1.170E-05
MDMA	81.8% (166/203)	88.4% (312/353)	6.62% [0.425; 13.3%]; 4.41; p = 0.0357	0.428; 0.0289
Amphetamine	16.3% (33/202)	28.7% (55/192)	12.3% [4.07; 20.4]; 8.576; p = 0.0034	0.534; 0.0107
Proportion (%) of samples with high sample content				
Comparison of samples from 2021 to 2011				**Linear regression from 2011 to 2021**
Substance	**Prop. in 2011 (%)**	**Prop. in 2021 (%)**	**Difference [95% CI]; X^2; p value**	**R^2; Pr > F**
Cocaine	44.7% (114/255)	90.2% (709/786)	45.5% [38.9; 51.8]; 240.406; p < 0.0001	0.829; 9.96E-05
MDMA	20.2% (24/119)	86.5% (166/192)	66.3% [56.5; 73.8]; 135.386; p < 0.0001	0.853; 4.98E-05
Amphetamine	11.2% (22/196)	55.3% (107/188)	44.1% [35.3; 52.0]; 84.433; p < 0.0001	0.929; 1.85E-06
Mean content of active ingredient (%; mg)				
Comparison of samples from 2021 to 2011				**Linear regression from 2011 to 2021**
Substance	**Mean (SD/n=) in 2011**	**Mean (SD/n=) in 2011**	**Difference ± SEM [95% CI]; t-statistic; p value**	**R^2; Pr > F**
Cocaine	51.8% (24.4/n=255)	81.6% (15.3/n=786)	29.7% ± 1.29 [27.2; 32.3]; 22.987; p < 0.0001	0.858; 4.283E-05
MDMA	100.2mg (27.5/n=119)	175.3mg (53.4/n=192)	75.1mg ± 5.28 [64.7; 85.5]; 14.211; p < 0.0001	0.910; 5.18E-06
Amphetamine	23.8% (23.6/n=196)	58.1% (32.1/n=188)	34.4% ± 2.87 [28.7; 40.0]); 11.968; p < 0.0001	0.908; 5.9E-06

SD= standard deviation; SEM= standard error of the mean; X^2= Chi-squared test; R^2= R-squared test.

in content may pose a risk to the health of the substance user, since a formal declaration of purity does not accompany the selling of these substances.

Although the study of adulterants in this retrospective data analysis is beyond the scope of this research and will be part of future research, we have added some examples with unexpected qualitative analytical findings (Fig. 4, E-I), as well as quantitative analytical findings with high levels of active ingredients (Fig. 4, A-D) of tested samples from 2021 among different galenic forms.

The authors would highlight the substance group of opioids, as DCS have recently expanded in Canada and the United States in response to the emerging global opioid epidemic that leads to substantial morbidity and mortality in North America and worldwide (Barocas et al., 2022; Hedegaard et al., 2020; Scarfone et al., 2022; Sherman et al., 2019). The number of complications due to injection drug use have risen, and in the past decade, heroin-related deaths in the US have quadrupled (Barocas et al., 2022; Hedegaard et al., 2020). It appears that the most common cause of death among people who use illicit opioids is accidental drug overdose, often by adulterated products with fentanyl and its analogues (Lewer et al., 2022). In our analysis it was demonstrated that the highest proportion of unexpected analytical results among all chemically analyzed substances by far was detected in injectable heroin samples, with a proportion of 99.3% (405/408). Among those, an alarmingly high proportion of samples was adulterated. In our study samples no adulteration with fentanyl was detected until 2021 and most adulterants consisted of acetaminophen (31%), caffeine (30%), codeine (20%), and morphine (15%) among others. Rigorous monitoring of this global trend through DCS will enable timely warnings to opioid users and public health officials if fentanyl adulterated opioids will reach Switzerland. Furthermore, there is some discussion within the published literature on the positive impact of DCS on the current opioid crisis in preventing those drug overdoses (Bardwell & Kerr, 2018; Karamouzian et al., 2018; Laing et al., 2018; Tupper et al., 2018). DCS for detecting adulterated opioids from unregulated markets could be a cornerstone in fighting the opioid pandemic and accessing this population. Importantly, the opioid crisis does not just affect opioids anymore. In the recent past fentanyl was also found in the non-opioid substances and sold with stimulants (e.g., cocaine, methamphetamine) (Jones et al., 2020). The increasing presence of synthetic opioids mixed into other illicit substances reflects the rapidly evolving nature of the opioid epidemic. This threat poses urgent and novel public health challenges which is especially concerning for people whose intent is to use non-opioids, and as they may be opioid naive, making drug checking services even more valuable to these individuals. Fortunately, conducting a search through our database until 2021, we have not found any samples of fentanyl adulterated cocaine or methamphetamine through DCS in Zurich. Further monitoring is of

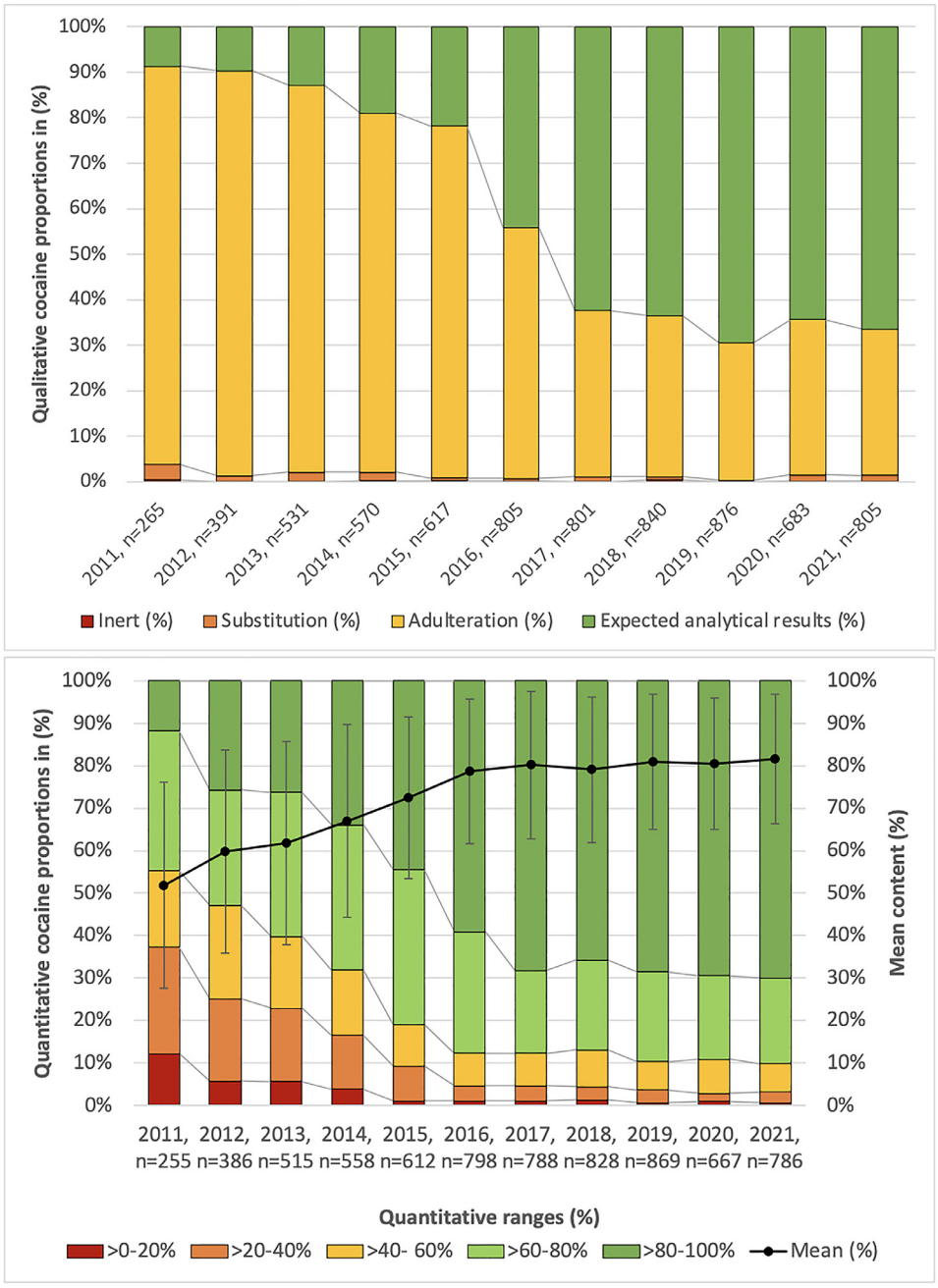

Fig. 5. Qualitative and quantitative development of declared cocaine per year at drug checking Zurich from 2011 to 2021.
Longitudinal qualitative (above) and quantitative (below) analysis of chemical test results of declared cocaine proportions at drug checking Zurich grouped by year during the observation period of 2011 to 2021 with their respective classifications and sub-classifications.

great importance to protect these substance users of this global development and inform them in a timely manner if this trend has reached Switzerland.

Within a decade of DCS in Zurich, it was shown that unregulated drug markets for different psychoactive substances were very dynamic. Drug checking can be used as a monitoring tool, as timely identification of newly arising substance trends can aid the adaption of prevention and harm reduction strategies.

The overall test capacity at DCS Zurich has increased over the decade, adapting to an increasing demand for DCS within the general population as well as increasing political support for this important public health intervention.

In this analysis, valuable qualitative and quantitative information has been provided on changes of analytical test results over time. In the longitudinal analysis of service user-provided MDMA, amphetamine, and cocaine, it was demonstrated significant uptrends in substance quality and contents over time were observed. Kerr and colleagues (Kerr et al. 2017) have previously hypothesized that it is reasonable to assume that DCS can help to shift the unregulated drug market towards providing a less toxic inventory as well as stabilizing the dynamic markets. By 'shifting and stabilizing' the unregulated drug market, users are at a lower risk of acquiring fraudulent and low-quality substances from a public health perspective. On an individual level, they are still left with an unpredictable uncertainty when consuming these substances, as significant adulteration is still common. There is no quality control over production and distribution of illegal substances, thus substance users must be protected from these fraudulent products. DCS offer a means of accountability in the illegal substance market that otherwise would not exist, since substance users who are able to receive feedback about what they are purchasing would be able to avoid patronizing dealers who sell fraudulent products. Our longitudinal data contributes to the body of evidence to further support the hypothesis of 'shifting and stabi-

lizing' the dynamic unregulated market. This must be interpreted with caution, as we only assessed samples provided by people using this service. There are many factors in the production and distribution chain of illicit substances that influence the drug market. Further studies are needed that examine the impact of DCS on the drug market. Furthermore, this is a retrospective data analysis, thus the effect of these findings on public health and individual health of users can only be hypothesized and need to be further explored in future studies. Evidence in the literature of the positive impact of DCS include improving drug-taking behavior and safer use, increasing knowledge among users, facilitating social support, accessing user populations, increasing risk awareness for recreational drug users and postponing the onset of first use, while not increasing or encouraging consumption or extending the circle of users (Hungerbuehler et al., 2011; Korf et al.. 2002; Maghsoudi et al., 2022; Measham & Turnbull, 2021; Measham, 2019). Despite all these findings, DCS still often take place in legal grey zones and are not accessible to many substance users. By 2017, a global review of DCS estimated the existence of only approximately 31 drug checking programs across 20 geographical locations, predominantly in Europe (Barratt et al, 2018). There is a great necessity for drug policy changes to make this service accessible in further settings and extend its reach to more users.

Among the included samples in this study, a substantial proportion (n=608, 3.71%) were declared "unknown" by the service-users, of which some samples are assumed to be provided by third parties. Although DCS are intended for people who use these substances, third party drug checking by dealers and suppliers, as well as other people, such as family members or friends occur frequently within DCS (Larnder et al., 2021). This service is not limited to people who use substances and may extend well beyond the using individual (Bardwell et al., 2019; Kerr & Tupper, 2017), as also DCS are often anonymous. Existing drug checking guidelines should be critically reviewed and further explored for the potential role in engaging people who sell drugs as a harm reduction practice with further reach to the drug distribution chain. This is particularly important as trust in the seller is still described to be the key criterion to protect users against these substances where DCS is not available (Bardwell et al., 2019; Brunt, 2017; Guirguis et al., 2020; Coomber et al., 2014).

Strengths and limitations

The strength of this study is that it constitutes one of the most extensive DCS database analyses with the biggest spectrum of different substances within the recently published peer-reviewed literature. This research comes with some limitations. The spectrum of included substances was limited to schedule 1, 2 and 3 drugs according to the controlled substance act (CSA), and no schedule 4 or 5 drugs were included for statistical analysis due to low sample size numbers of individual substance groups. Although using the scheduling system under the CSA for this study, this classification system comes with limitations, as it is inaccurate and outdated for certain substances. For example, according to current knowledge, neither DMT, nor psilocybin have any high abuse potential, thus should not be considered as schedule 1 drugs (Nutt et al., 2007). Additionally, the classification system is not unified across different geographical locations.

Furthermore, the database was initially not designed as a research tool; thus, data acquisition and documentation has changed over time and was not standardized for a long time. Also, methodological factors may have led to some bias within this study, such as analytical changes over time (e.g., chemical analysis, measuring different salt forms or hydrated forms), and definitions of quantity and quality used for this research. This may have resulted in some missing data and wrongfully declared and/or extracted data and subsequently some over- or underestimation of certain proportions within our results. In regard to measuring different salt forms and hydrated forms, this was accounted for within the chemical and statistical analysis process, although small uncertainties remain which is a limitation of these analytical systems, yet some variations are expected and to be tolerated.

Furthermore, this study is a single-site analysis and only describes the scope of substances found within one location in Switzerland. Although a comparison of analytical test results across different drug checking services and countries would be of great interest to compare testing trends, this is beyond the scope of this current research. The European monitoring centre for drugs and drug addiction (EMCDDA) and other authors have attempted an international comparison of quantitative and qualitative analytical test results and demonstrated similar analytical trends across different locations, with differences per country side (Brunt & Niesink, 2011; European Drug Report, 2020). These analyses are challenged by many factors, including different analytical testing procedures, ways of extraction, measuring to the base or salt form, classifications, quantification method used among many more across different DCS locations. Future research should focus on combining information from various DCS across different locations, incorporating these differences to compare standardized results.

Conclusions

With this article, we demonstrate that over half of substances acquired from unregulated drug markets analyzed through DCS Zurich that were provided by service-users include sample with unexpected and low sample contents. This puts substance users in a situation of unpredictable uncertainty as they are exposed to unexpected harms and these samples are potential individual and public health threats. Furthermore, it was demonstrated that the unregulated drug market for psychoactive substances is very dynamic, underlining the need to continue to monitor these markets. This analysis contributes to the body of evidence that DCS may have the potential to 'shift and stabilize' unregulated drug markets towards providing better quality substances to a certain extent. Our study results emphasize the need of DCS as an important monitoring tool for public health officials. The positive impact of our findings on individual and public health can only be hypothesized as this was a retrospective data analysis. Further studies towards DCS and its ability at harm reduction are needed that focus on substance use and health outcomes of substance users. The necessity for drug policy changes to make this service accessible in further settings and more users was highlighted as DCS still often take place in legal grey zones.

Contributors

RM/DS conceived of the review. RM conducted the literature search. RM/MS extracted the data. DS/MS provided methodological expertise. DT provided methodological expertise on chemical analysis of the samples. DT and his team performed the chemical analyses. RM conducted the statistical analysis. RM created the manuscript draft. All authors contributed to refinement of the manuscript and approved the final manuscript.

Ethics approval

The authors declare that the work reported herein did not require ethics approval because it did not involve animal or human participation.

Declarations of Interest

The authors declare that they have no competing interests.

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DIZ group

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ReseaChem GmbH group

Isabelle Minder, Juri Schiltknecht, Konrad Uhlmann, Marcel Hadorn, Martina Lengacher, Nicole Bolzli, Seila Eggimann, Tamara Wüthrich

Supplementary materials

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