Adulteration of low-delta-9-tetrahydrocannabinol products with synthetic cannabinoids: Results from drug checking services

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Abstract
Since late 2019, low-delta-9-tetrahydrocannabinol (THC) preparations adulterated with synthetic cannabinoids (SCs) have been frequently observed in Switzerland. The unawareness of users concerning the presence of SCs and the typically higher potency and toxicity of SCs, when compared with THC, can result in increased health risks. In Switzerland, low-THC (<1%) cannabis products, except hashish, are legal. These products can act as carrier materials for SCs. In this study, cannabis samples and user self-reports received through three drug checking services were collected and analysed, to gain deeper insight into this new phenomenon. Samples were collected from January 2020 to July 2021. Liquid chromatography coupled with high-resolution mass spectrometry was used for the qualitative screening and semi-quantification of SCs, while gas chromatography with flame ionization detector was applied for the quantification of THC and cannabidiol levels. Reported adverse effects were compared between users who consumed adulterated (SC-group) and non-adulterated (THC-group) products. Of a total 94 samples, 50% contained up to three different SCs. MDMB-4en-PINACA was most often detected. All adulterated cannabis flowers contained ≤1% THC. Adulterated hashish also typically presented low THC-levels (median: 0.8%). The SC-group was associated with higher numbers of adverse events (p = 0.041). Furthermore, psychologic (p = 0.0007) and cardiologic (p = 0.020) adverse effects were more profound in the SC-group than in the THC-group. Drug checking services enabled the timely detection and monitoring of new and potentially dangerous trends. Furthermore, due to user-reports, additional valuable information was gained on adverse events associated with the consumption of novel SCs.

Keywords
adverse effects, drug checking, high-resolution mass spectrometry, market monitoring, synthetic cannabinoids
1 | INTRODUCTION

1.1 | Background and aims

Synthetic cannabinoids (SCs) currently comprise the largest substance class within the group of new psychoactive substances (NPS). However, data on the pharmacology and toxicology of NPS, such as SCs, are generally scarce. Data on NPS are obtained through case reports and series, poisons information centres, online forums, and surveys. However, the lack of analytical confirmation of the consumed product is often a serious limitation. In order to monitor illegal markets and detect new trends, seized material from forensic casework or products obtained via online test purchase are investigated. In contrast to studies examining user reports, these instances will give no information on pharmacodynamics or toxicological effects. Drug checking services offer valuable insights into the drug market often including user self-reports describing the drug’s effects. For instance, Oomen et al. recently highlighted the importance of drug checking services for the monitoring of new trends, demonstrated by the example of adulterated cannabis products.

This study presents data, gained through drug checking services, and elucidates the new phenomenon of low-THC cannabis preparations adulterated with synthetic cannabinoids (SCs). Study aims are to inform on present developments, with regard to identified compounds, applied carrier material, and reported adverse effects after consumption of adulterated cannabis products. As both adulterated as well untreated drug-type cannabis (high-THC) samples were handed-in, this offered the opportunity to compare reported adverse effects between drug-type cannabis (THC-group) and SCs (SC-group). This study underlines the potential of drug checking services to act as a market monitoring tool as well as source of information on effects of NPS.

1.2 | Synthetic cannabinoids

Since the emergence of SCs on the recreational drug market in 2008, 209 SCs are being monitored by the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA), illustrating the considerable variety of compounds belonging to this class. Most SCs show high binding affinities and demonstrated activities at the cannabinoid receptors 1 and 2 (CB1 and CB2). Therefore, many SCs have similar cannabimimetic effects as tetrahydrocannabinol (THC), the main psychoactive ingredient of THC-rich cannabis. The psychoactive effects of THC are mostly attributed to the binding and activation of CB1. SCs are often associated with much higher potency and toxicity when compared with THC, resulting in increased health risks for individuals and escalated public health concerns. Since their emergence on the drug market, numerous cases of severe intoxication, including lethal outcomes, have been associated with SC uptake. The EMCDDA issued a report in 2020, stating a total of 768 seizures of the SC MDMB-4en-PINACA in 20 member states. This illustrates the extensive availability of MDMB-4en-PINACA, which made its first appearance on the drug market in 2018. A transnational study conducted by Norman et al. found MDMB-4en-PINACA to be one of the most popular SCs by end of September 2020, while comparing SC prevalence in prisons and in the wider population in Germany, the United Kingdom, and the United States. However, the aforementioned authors also observed significant regional differences in the identified SCs, probably resulting from local supply networks and differences in legislation. It is believed that the legal frameworks in China, thought to be the main production site of many SCs, influence the emergence and availability of SCs on the European market.

1.3 | Drug checking services

Switzerland, as well as other European countries, has a long history of drug checking services, with the first of these services being introduced in the 1990s. Drug checking services are low threshold harm reduction services, which offer recreational drug users the possibility to subject their samples to chemical analysis without legal consequences. The drug test results obtained from drug checking services generally include identity and quantity of the main active ingredient as well as any pharmacologically relevant adulterants and, in cases of fixed dosage forms (i.e., tablets and trips), the respective dosages. Drug checking services offer an insight into the recreational drug market at consumer level and, thus, act as a market monitoring tool. Drug checking services range from onsite (mobile) testing at festivals or nightclubs to stationary premises. The analytical methods, and, therefore, the reliability of results, may vary considerably between these services. Mass spectrometric techniques are considered the gold standard in regards of specificity and sensitivity, however, due to the technical requirements of the instruments (i.e., gas supply, electricity, and ambient conditions), mass spectrometry is typically limited to stationary settings.

1.4 | Low-THC cannabis products: regulatory and clinical aspects

Low-THC cannabis products are defined by the EMCDDA as “products being or containing cannabis herb, resin, extracts or oils that claim or appear to have a very low percentage of THC and which would be unlikely to cause intoxication.” The regulatory limit for THC varies between national drug policies, with Switzerland applying a higher threshold than most European countries (e.g., 0.2%). Swiss law allows the production, selling, and possession of cannabis products (including plants, dried cannabis flowers, oils, and tinctures) with a THC content of <1%, with the exception of hashish (cannabis resin)—the latter being considered illegal, regardless of its THC content. In 2011, in order to facilitate industrial hemp production, the threshold for THC was increased from 0.3% to 1%, ultimately resulting in an emerging market for low-THC cannabis products, including dried cannabis flowers, regulated as tobacco substitutes.
In recent years, a growing industry around low-THC and high-cannabidiol (CBD) products, often referred to as “CBD-products” with the main focus on CBD-oils, has been observed globally. \cite{38,39,41,42} The selling of low-THC cannabis herbs has also been reported for some European countries. \cite{38,43} Information on legal frameworks and market trends surrounding low-THC cannabis products on a cross-national level has been extensively reviewed and reported by McGregor et al.\cite{39}

For low-THC cannabis products, fibre-type varieties of cannabis (industrial hemp) are often used, due to higher levels of CBD being present in these materials when compared with those found in drug-type cannabis.\cite{26,39,42} CBD and THC are the main and best-characterized phytocannabinoids of the cannabis plant.\cite{26,41,42,44} CBD is considered non-intoxicating and has been recommended for several therapeutic applications.\cite{44} Nevertheless, clinical studies systematically investigating therapeutic effects of CBD are limited, resulting in little evidence of CBD’s medical benefits and, therefore, requiring further research.\cite{41,42} Purified CBD is widely considered to be safe and well tolerated.\cite{39,44} In Switzerland, low-THC cannabis flowers are typically smoked with and without addition of tobacco, thus, the transferability of results obtained for medicinal CBD products is limited due to differences in the route of administration and dosage.\cite{64} However, due to the lack of intoxicating effects of CBD and the low percentage of THC, no intoxicating effects as in drug-type cannabis are expected for low-THC cannabis products.\cite{39,45}

1.5 | Low-THC-cannabis products: challenges

The availability of legal low-THC cannabis flowers and derived products has resulted in several challenges, including concerns around the ability to distinguish between low- and high-THC cannabis plant material. The Swiss police addressed this by introducing a rapid reagent test, enabling the distinction between low- and high-THC products.\cite{38,46} Further questions arose concerning driving ability after intake of low-THC products.\cite{43,45,47} In parallel, an additional challenge has emerged: the adulteration of low-THC cannabis products with SCs.\cite{130} Since late 2019, increasing numbers of cannabis preparations adulterated with SCs have been reported in Switzerland, with both forensic institutions and drug checking services contributing to the detection and monitoring of this new trend.\cite{30} These adulterated cannabis products, which are neither visually nor olfactorily distinguishable from regular cannabis products, are typically sold as regular high-THC cannabis flowers and hashish and thus leave recreational cannabis users uninformed of adulteration. The generally higher potency of SCs, when compared with THC, and the user’s unawareness of the presence of SCs result in an increased potential for intoxications and health risks.\cite{3,6} This is further aggravated by the fact that little is known about the pharmacology and short- and long-term toxicity of most SCs.\cite{6,17} Regarding the SC adulterated products, consumer risk is further exacerbated by unknown SC content and potential inhomogeneity.\cite{17}

In response to the emerging health risks, the public were informed and warned via several media releases.\cite{38–50} Oomen et al.\cite{22} recently presented data gained from different European drug checking services, including one Swiss drug checking service, on cannabis products adulterated with the SC MDMB-4en-PINACA. It was shown that even though first detected in Switzerland, adulterated cannabis products have been detected in other countries as well, for instance Italy, Germany, France, and Austria.

2 | MATERIAL AND METHODS

2.1 | Sample and data collection

Cannabis samples were collected between January 2020 and July 2021 at stationary drug checking services in three cities in Switzerland (Basel: DIBS, Lucerne: DILU, Olten: Suchthilfe Ost). Users of the drug checking services were obligated to undertake professional counselling in order to have their sample analysed. The entire drug checking process is fully anonymous, meaning that no personal information (e.g., name, date of birth, visual nature, address, and phone number) is collected. Therefore, all data received from the drug checking services were fully anonymised at the time point of data collection, leaving no possibility to trace back individuals. Consequently, according to Swiss national legal standards, this study did not require formal ethics approval.

During sample collection, the visitors were routinely questioned on sample-specific information, including the alleged identity and dosage of the product. The volunteers were further asked if they had already consumed the product and, if consumption was affirmed, they were asked for additional detail on their experience (e.g., adverse effects, effect duration, potency, and further observations). These self-reports were noted by means of free text by staff at the drug checking centre. After analysis, the users received their results anonymously via phone. For this, the user called the drug checking centre while hiding their phone number and mentioned a password that was defined during counselling. For cannabis material, results included presence and identity of detected SCs and estimation of cannabis type (high- versus low-THC). All remaining material was stored at room temperature in a dark storage area and preserved in individual pressure lock bags. To expand the scientific impact of this study, the samples (where sufficient material was available) were subjected to additional THC and CBD quantification and semi-quantification of selected SCs.

2.2 | Evaluation of reported adverse effects

Prior to the statistical evaluation of the reported adverse effects and further experiences (e.g., short effect duration), the self-reports were randomized. The reported side-effects and experiences were designated to applicable categories by a different scientific employee, while remaining uninformed about the analytical results,
that is, if a sample was adulterated or not. For the comparison of the occurrence of adverse events, the individual reports were classified into the categories “adverse event” or “no adverse event.” The latter was chosen in cases where the drug’s effects were described as “normal” or “potent,” therefore lacking in apparent unwanted effects. Adverse events were further evaluated by sorting them into pharmacologic subcategories. The subcategory “cardiovascular adverse effects” included palpitations, circulatory collapse, circulatory issues, and chest discomfort. For “neurologic adverse effects,” paraesthesia, seizure, muscular cramps, paralysis, agitation, dizziness, headache, unconsciousness, and vomiting were considered. The subcategory “psychologic adverse effects” comprised strong psychodelic effects (for example hallucination), anxiety and paranoia, panic attacks, general psychologic discomfort and stress, as well as disorientation. For each subcategory, one or more of the above-mentioned symptoms had to be met for an adverse effect subcategory to be considered as confirmed. Independency testing of the occurrence of adverse events, adverse effect subcategories, and other experiences, enabling the comparison between the THC- and SC-group, was performed using the Fisher’s exact test. Statistical testing and calculation of odds ratios (ORs) and 95% confidence intervals (95% CIs) were conducted in R (version 3.4.3) using the fisher.test function.

2.3 | Chemicals and analytical reference material

LC-MS grade methanol (MeOH), water, and acetonitrile (ACN) were purchased from Macherey-Nagel AG (Oensingen, Switzerland). Formic acid (98-100%), analytical grade ethylacetate (EtOAc) with purity ≥99.0%, docosane analytical standard with purity >99.9%, and analytical grade warfarin (4-hydroxy-3-(3-oxo-1-phenylbutyl)-purity ≥99.0%, docosane analytical standard with purity >99.9%, and analytical grade warfarin (4-hydroxy-3-(3-oxo-1-phenylbutyl)-cumarin) with purity ≥98.0% were obtained from Merck (Zug, Switzerland). Certified reference standards of d,l-11-nor-delta-9-THC (THC), d,l-11-nor-delta-9-THC carboxylic acid (THCA), cannabidiol (CBD), and cannabidiolic acid (CBD) were obtained from Lipomed AG (Arlesheim, Switzerland).

Reference material for SCs was obtained from Cayman Chemical Company (Michigan, USA), Lipomed AG (Arlesheim, Switzerland), or provided either by the Zurich Forensic Science Institute (Zurich, Switzerland) or the State Criminal Investigation Office Baden-Württemberg (Stuttgart, Germany)—for detailed information, see Table S1

2.4 | Homogenization and sampling

Prior to analysis, flower samples were homogenized using a grinder, after removal of larger branches. Hashish samples were finely cut using a scalpel. In order to achieve a mean value for the SC and phytocannabinoid contents, the whole sample was homogenized before weighing for the respective analyses.

2.5 | Qualitative screening for SCs

For screening of the SCs, 1 ml MeOH containing the internal standard (ISTD) warfarin at 0.25 mg/ml was added to 50 mg of homogenized sample. Warfarin was chosen as ISTD instead of a deuterated SC, due to the relatively large quantities required for this analytical method and associated costs. Samples were vortexed for 10 s and filtered using Simplepure™ syringe filters (13 mm, 0.45 μm) obtained from BGB Analytik AG (Boeckten, Switzerland). Finally, the extracts were diluted 1:10,000 in MeOH.

All instrumentation and the analytical column described in the following sections were obtained from Thermo Fisher Scientific™ (Reinach, Switzerland). For chromatographic separation, a Dionex Ultimate 3000 RS ultra UHPLC system was used equipped with a Hypersil™ Phenyl analytical column (1.9 μm, 100 × 2.1 mm), kept at 30°C by a MultiSLEEVE™ column heater. The injection volume was 5 μl and the total flow rate 0.6 ml/min. The gradient started at 80% mobile phase A, consisting of 0.1% (v/v) formic acid in water, and 20% mobile phase B, comprised of 0.1% (v/v) formic acid in ACN. The percentage of mobile phase B was increased over 0.92 min to 40%, after which it was increased further to 71% over 6 min, and finally ramped to 100% over 0.25 min. This setting was held for 1 min, after which the system was allowed to re-equilibrate to the initial settings for 1.25 min, resulting in a total run time of less than 10 min per sample.

Subsequent analysis was conducted using a Thermo Scientific™ Q Exactive™ HF Hybrid Quadrupole-Orbitrap™ mass spectrometer operated with a heated electrospray ionization (H-ESI) source in positive ionization mode. A sheath gas flow rate of 50 arbitrary units (AU) and auxiliary gas flow rate of 5 AU were applied. The spray voltage was +3.5 kV, and the capillary temperature and auxiliary gas heater temperature were 200°C and 300°C, respectively. A full scan measurement from m/z 150 to m/z 1000 was conducted at a resolution of 120,000 full width at half-maximum (FWHM) at m/z 200. Automatic gain control (AGC) target was set to 3e6, and maximum injection time (IT) was 200 ms. Data acquisition and evaluation was conducted using the Tracefinder™ (version 5.1, Thermo Scientific™) software. With a mass error 5 ppm and detection windows of 30 s, exact mass signal and retention times were used for qualitative identification. Besides SCs, the natural cannabinoids THCA, THC, CBD, and CBDA were additionally detected to compare the respective areas—enabling a rough estimation of the cannabis type. This estimation was based on comparison on the ratio of the total peak areas of THC and CBD, areaTHC + areaCBD / areaCBD + areaTHC. High-THC and low-CBD samples were defined for ratios >1, high-CBD and low-THC for samples with ratios <1, while a ratio of approximately 1 was estimated as intermediate type. Screened [M + H]+ and retention times are listed in Table S2. Prior to every sequence, a quality control (QC) sample was injected containing a mixture (see Table S1) of all 63 SCs validated for the qualitative screening at 5 ng/ml to assure functionality and performance of the analysis.

In order to screen for novel SCs, for which no reference material was available at the time of analysis, and to retrospectively search for SCs which have only recently entered the drug market and were,
therefore, not known at the time of analysis, data were also manually screened using the software FreeStyle™ (version 1.7, SP1, Thermo Scientific™). This was conducted by investigating the data for corresponding [M + H]+ (mass error 5 ppm) signals. Signals corresponding to novel SCs were further investigated applying data dependent MS² measurements (dd-MS²) at resolutions of 60,000 FWHM (Full MS) and 15,000 FWHM (MS²), with normalized stepped collision energies of 10, 17.5, and 35 (normalized to m/z 500 [z = 1]). Where available, the MS² spectra were compared with published product ion spectra. To confirm the obtained results, reference materials (where available) were obtained, allowing full verification of the result.

The screening method for SCs was validated concerning limit of detection (LOD), specificity, and selectivity for 63 SCs (status: June 2021, Table S2). The respective LODs were determined in both the matrix (spiked pool of six hashish and six cannabis flower extracts) and MeOH. LODs were investigated using FreeStyle™ (version 1.7, SP1, Thermo Scientific™) software. The formal criterion for LODs was signal to noise (S/N) of greater than three to one, although, due to the applied low noise system, much higher S/N at LOD were achieved.

Specificity and selectivity were verified by measuring six hashish and six cannabis flower preparations (low- and high-THC), accompanied by investigation of injections of mixtures and individual SCs, with a focus on the resolution and distinction of structural isomers (e.g. 5F-MDMB-PICA and 5F-MDMB-P7AICA), isobaric compounds, and possible interfering signals (i.e., isotopes). The recoveries of the herein applied sample preparation procedure (filtration and dilution) were evaluated by applying a spiking experiment. This experiment was conducted with three SCs (5F-MDMB-PICA, 4F-MDMB-BINACA, and MDMB-4en-PINACA), as sufficient amounts of reference material were available for these compounds. In brief, 50 mg of low-THC cannabis flowers were spiked in triplicates using standard solutions of the respective SCs at concentrations translating to 5 μg/mg plant material (0.25 mg/ml) to which ISTD was added (0.25 mg/ml). The area ratios obtained after sample preparation were compared with the ratios obtained after direct dilution of the analytical standards in MeOH.

2.6 | Semi-quantification of selected SCs

5F-MDMB-PICA, 4F-MDMB-BINACA, MDMB-4en-PINACA, and ADB-BUTINACA, which were most frequently detected in this study (≥4 detections), were additionally subjected to semi-quantification. Therefore, the previously described screening method was expanded. In a preliminary experiment investigating the influence of the matrix, calibrator solutions (5 ng/ml, 25 ng/ml, 50 ng/ml, and 75 ng/ml translating to 1 μg/mg, 5 μg/mg, 10 μg/mg, and 15 μg/mg with a dilution-factor of 1:10,000) were prepared in matrix (diluted low-THC cannabis flower extract) and MeOH (solvent). Recoveries were calculated via comparison of area ratios obtained in matrix and solvent. The calibrators (levels as described above) used for semi-quantification were prepared in solvent. In addition to the initial screening, samples were also subject to semi-quantification, where sufficient sample material was available. In cases where the signal was below the lowest calibrator, the sample was remeasured applying a smaller dilution factor. For semi-quantification the TraceFinder™ (version 5.1, Thermo Scientific™), software was used. The respective semi-quantitative contents for each SC were calculated by comparison of area ratios between sample and calibration curve (internal standard method).

2.7 | Quantification of THC and CBD

For the quantification of THC and CBD, an accredited method (according to the guidelines of the Swiss Society of Forensic Medicine, SGRM[5]), routinely applied for the forensic chemical analysis of cannabis material, was used. LODs and limits of quantification (LOQs) are 0.1% (w/w, corresponding to 1 mg/g) and 0.3% (w/w, corresponding to 3 mg/g) for both analytes, CBD and THC, respectively. The homogenized samples were weighed (30–50 mg) into 4-ml glass screw top vials obtained from BGB Analytik AG (Boeckten, Switzerland) to which 2 ml ISTD-solution (0.5 mg/ml docosane in EtOAc) was added. After sonification for 15 min at room temperature, using a SW3H ultrasonic bath from Sonoswiss AG (Ramsen, Switzerland), the extracts were set aside for 10 min to allow insoluble parts to settle. The supernatant was then diluted 4:1 with EtOAc, resulting in a final concentration of the ISTD-solution of 0.125 mg/ml. For the subsequent analysis, 1 μl of the diluted sample was injected using an AI 3000 autosampler from Thermo Fisher Scientific™ (Reinach, Switzerland). The Inlet temperature was 210°C, and the split/splitless (SSL) injector was operated with a split ratio of 1:50. Chromatographic separation and analysis were achieved using a FOCUS GC gas chromatograph with flame ionization detector (FID), obtained from Thermo Fisher Scientific™ (Reinach, Switzerland). For the chromatographic separation, an Agilent J&W DB-5MS column (15 m × 0.250 mm, inner diameter 0.25 μm) was used. Starting temperature of the GC oven was 120°C. This temperature was held for 2 min after which it was ramped at 15°C/min until the final temperature of 280°C was reached, which then was held for further 2 min. The GC was used in constant flow mode at a flow rate of 0.8 ml/min with helium as carrier gas. The FID detector was operated at 300°C with nitrogen as makeup gas. Quantitative results were calculated using the analyte/internal standard response ratio.

3 | RESULTS AND DISCUSSION

3.1 | Validation of the SCs screening method

In the measured solutions, the LODs ranged from 0.3 ng/ml to 0.6 ng/ml, with the exception of ADB-PINACA (LOD = 2 ng/ml), translating into concentrations at the product level, when applying a 1:10,000 dilution factor, of 0.06 μg/mg and 0.12 μg/mg, respectively (analyte loss during sample preparation not considered). LODs and respective S/N ratios at LOD are summarized in Table S2. The spiking...
experiment revealed mean recoveries of 94.4 ± 1.7%, 99.5 ± 0.5%, and 103.8 ± 2.1%, for 5F-MDMB-PICA, 4F-MDMB-BINACA, and MDMB-4en-PINACA, respectively.

### 3.2 SCs prevalence over time

Of all cannabis samples \((n = 94)\), 50\% \((n = 47)\) were found to contain up to three, of the following SCs, namely, 4F-MDMB-BICA (4F-MDMB-BUTICA), 4F-MDMB-BINACA, 5F-MDMB-PICA (5F-MDMB-2201), 5F-MDMB-PINACA (5F-ADB), ADB-BUTINACA (ADB-BINACA), MPHP-2201 (5F-MPP-PICA, 5F-MPhP-PICA), and MDMB-4en-PINACA. Structures of all herein detected SCs are presented in Figure 1. The absolute numbers of detections for each SCs over time are presented in Figure 2 and listed in Table 1.

Mixtures were merely applied onto cannabis flowers, while hashish was always adulterated using a single SC. A tendency from mixtures towards the use of single SCs was observed for cannabis flowers in this study. Of all SC positive cannabis flowers collected in 2020 \((n = 17)\), 47\% \((n = 8)\) contained mixtures of up to three different SCs. In the first half of 2021, the percentage of cannabis flowers containing more than one SC decreased to 25\% \((n = 2)\), with mixtures containing a maximum of two SCs.

MDMB-4en-PINACA was most commonly found. It was detected in 40\% \((n = 38)\) of all analysed cannabis samples \((n = 94)\) and in 81\% \((n = 38)\) of all adulterated samples \((n = 47)\), including mixtures. Oomen et al.\textsuperscript{22} reported the presence of the SC MDMB-4en-PINACA in 23.6\% \((n = 270)\) of all analysed cannabis samples collected at various drug checking services throughout Europe.

Regarding the collected data about MDMB-4en-PINACA, 5F-MDMB-PICA, and 4F-MDMB-BINACA, in 2020, the results of this study match previously reported SC prevalence on transnational levels.\textsuperscript{12,20,52,53} Over the period of this study, 4F-MDMB-BINACA and 5F-MDMB-PICA were only detected as adulterants in 2020. The ever-changing SCs market is also illustrated in this study by the first detection of ADB-BUTINACA in February 2021. ADB-BUTINACA has since been repeatedly detected, with additional seven detections in the timeframe up to the end of June 2021 (end of study). The emergence of ADB-BUTINACA has also been reported in other countries.\textsuperscript{22,54,55} Thus, ADB-BUTINACA could become increasingly popular on the drug market in the near future and replace earlier SCs.

### 3.3 Semi-quantification of selected SCs

When comparing the area ratios obtained in matrix and solvent, mean recoveries of 97.5 ± 4.0%, 102.8 ± 1.5%, 98.4 ± 1.9%, and 92.6 ± 4.6% were achieved for 5FMDMB-PICA, 4F-MDMB-BINACA, MDMB-4en-PINACA, and ADB-BUTINACA, respectively. The correlation factors of all calibrations used for semi-quantification were >0.998.

Of the adulterated samples, 79\% \((n = 37)\) were subjected to semi-quantification. Mean values and standard deviations (SDs) of 2.0 ± 1.1 \(\mu g/mg\) (range 0.6–4.2 \(\mu g/mg\)), 4.3 ± 2.2 \(\mu g/mg\) (range 0.1–7.2 \(\mu g/mg\)), 5.6 ± 2.2 \(\mu g/mg\) (range 1.0–9.9 \(\mu g/mg\)), and 2.5 \(\mu g/mg\) (only quantifiable in one sample) were found for 5F-MDMB-PICA, MDMB-4en-PINACA, ADB-BUTINACA, and 4F-MDMB-BINACA, respectively. The highest SC concentrations were detected for ADB-BUTINACA. The SC and phytocannabinoid contents are summarized in Table 1. Two cannabis flower samples (14 and 22) contained 4F-MDMB-BINACA and MDMB-4en-PINACA, respectively, in trace amounts. The low contents probably originated from contamination during manufacturing, ultimately resulting in signals below limit of quantification (LOQ). Previous studies reported SC contents for herbal

![Chemical structures of detected SCs](image-url)
blends ("spice") of different SCs than detected in the presented study. Direct comparability of quantitative results is difficult. For instance, differences in the potency of SCs might influence required dosages. Despite the existence of data on potency and efficacy of selected SCs at CB1, one drawback is the limited comparability between different in vitro assays. Further, pharmacokinetic parameters of SCs are largely unknown, ultimately rendering dose estimates currently unfeasible. Concerning the herein detected SCs, Cannaert et al. reported EC50 values at CB1, obtained via a β-Arrestin 2 recruitment assay, for 5F-MDMB-PICA (3.26 nM), MDMB-4en-PINACA (2.33 nM), 4F-MDMB-BINACA (7.39 nM), ADB-BUTINACA (6.36 nM), 5F-MDMB-PINACA (1.78 nM), MPHP-2201 (32.9 nM), and 4F-MDMB-BICA (121 nM). Therefore, the SCs detected in this study presented high potencies at CB1 in the mid- to low-nM range. The overall seemingly lower contents detected in this study, when compared with earlier results for spice preparations, may be explained by the dosages being adjusted, as the adulterated products encountered in this study are intended to mimic regular cannabis preparations; thus, the effects should comply as closely as possible with those encountered from THC-rich cannabis preparations.

A study conducted in 2014 by Moosmann et al. investigated the SC contents in 311 herbal blends from 31 different brands. Considerable inter- and intra-package variances in SC contents were shown, ultimately resulting in increased risks for accidental overdosing. A study from 2019, addressing the same question via the analysis of 20 herbal blends, presented less variation, indicating that the risk for consumers has slightly decreased. Inhomogeneities regarding SC content were also expected in this study, especially in the case of adulterated cannabis flowers, which presumably are sprayed during adulteration. This would likely result in uneven distribution of SCs, given the morphologic shape of cannabis flowers. For MDMB-4en-PINACA, however, eight hashish samples showing strikingly similar contents of MDMB-4en-PINACA with mean value of 6.5 ± 0.3 μg/mg were detected between December 2020 and June 2021 (formatted bold in Table 1). These products, obtained over an interval of half a year, showed varying CBD und THC contents, thus implying different production batches. It can be hypothesized that the producer(s) applied a standardized process, which resulted in reproducible SC contents—however, this will need to be proven by further studies.

### 3.4 | Carrier material

A total of 94 cannabis samples, comprised of 55% cannabis flowers (n = 52) and 45% hashish (n = 42), were collected during the time course of this study. Of all adulterated samples (n = 47), 53% (n = 25) were cannabis flowers, and 47% (n = 22) were hashish. For the adulterated hashish samples, the presence of trichomes, demonstrating that the samples originated from cannabis plant material, was verified applying microscopy (data not shown). Figure 3 shows the distribution over time of the adulterated carrier material. In the first three quarters of 2020, cannabis flowers were predominantly handed in for analysis. All adulterated cannabis flowers, where sufficient sample material enabled natural cannabinoid quantification, presented low THC and high CBD contents (in relation to each other), with mean THC and CBD concentrations of 0.6% (range <0.3–1%) and 14% (range 2.7–19.3%), respectively. In consideration of the Swiss harmonized measurement uncertainty, published by the SGRM, the obtained THC-values of the analysed cannabis flowers were below the Swiss legal THC threshold of 1%. The presented results are in accordance with recently published data on the phytocannabinoid contents of cannabis flowers adulterated with the SC MDMB-4en-PINACA. The use of low-THC cannabis flowers might be explained as that, in the view of producers, it is attractive to obtain and store a legal product (low-THC cannabis flowers), which is then altered into a psychoactive and illegal product only prior to releasing the product on to the market. The adulterated low-THC cannabis flowers are not distinguishable from the non-altered cannabis by the routinely used colour reagent test used by the Swiss police. Therefore, those products are less likely to be detected by police forces as the test result will indicate a supposedly legal product.

Additionally, economic motives might have promoted the production of adulterated cannabis products, as the market price of low-THC cannabis flowers is typically lower than that of (illegal) high-THC...
**TABLE 1**  Quantitative results for CBD and THC (percentage w/w) and semi-quantitative results for SCs

(A)

| Cannabis flower sample | Period   | THC (%) | CBD (%) | 5F-MDMB-PICA (μg/mg) | MDMB-4en-PINACA (μg/mg) | ADB-BUTINACA (μg/mg) | 4F-MDMB-BINACA (μg/mg) | 4F-MDMB-BICA (qualitative) | 5F-MDMB-PINACA (qualitative) | 5F-MPHP-2201 (qualitative) |
|------------------------|----------|---------|---------|-----------------------|--------------------------|----------------------|-------------------------|----------------------------|----------------------------|----------------------------|
| 1                      | Q1 2020  | -       | -       | >LOD<sup>a</sup>     | >LOD<sup>a</sup>         | n.d.                 | >LOD<sup>a</sup>         | n.d.                       | n.d.                       | n.d.                       |
| 2                      | Q1 2020  | 0.6     | 18.1    | 0.6                  | 0.3                      | n.d.                 | 2.5                     | n.d.                       | n.d.                       | n.d.                       |
| 3                      | Q2 2020  | 0.3     | 8.5     | 2.0                  | n.d.                    | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 4                      | Q2 2020  | 0.5     | 14.4    | n.d.                 | n.d.                    | n.d.                 | n.d.                    | >LOD<sup>b</sup>           | n.d.                       | n.d.                       |
| 5                      | Q3 2020  | 0.5     | 12.5    | 1.4                  | 4.5                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 6                      | Q3 2020  | 0.7     | 17.1    | n.d.                 | n.d.                    | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 7                      | Q3 2020  | 0.7     | 19.3    | n.d.                 | 3.2                      | n.d.                 | >LOD<sup>b</sup>         | n.d.                       | >LOD<sup>b</sup>           | n.d.                       |
| 8                      | Q3 2020  | 0.6     | 10.6    | n.d.                 | 1.8                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 9                      | Q3 2020  | -       | -       | n.d.                 | >LOD<sup>a</sup>         | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 10                     | Q3 2020  | 0.6     | 18.4    | >LOD<sup>a</sup>     | >LOD<sup>a</sup>         | n.d.                 | >LOD<sup>a</sup>         | n.d.                       | n.d.                       | n.d.                       |
| 11                     | Q3 2020  | 0.6     | 12.1    | n.d.                 | 4.6                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 12                     | Q3 2020  | 0.7     | 13.1    | 2.4                  | n.d.                    | n.d.                 | >LOD<sup>b</sup>         | n.d.                       | n.d.                       | n.d.                       |
| 13                     | Q3 2020  | 0.6     | 13.4    | n.d.                 | 3.0                      | n.d.                 | >LOD<sup>b</sup>         | n.d.                       | >LOD<sup>b</sup>           | n.d.                       |
| 14                     | Q4 2020  | 0.7     | 14.1    | 1.1                  | 1.1                      | n.d.                 | <LOQ                    | n.d.                       | n.d.                       | n.d.                       |
| 15                     | Q4 2020  | 0.9     | 16.4    | n.d.                 | 2.2                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 16                     | Q4 2020  | 0.5     | 12.8    | n.d.                 | >LOD<sup>a</sup>         | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 17                     | Q1 2021  | -       | -       | n.d.                 | >LOD<sup>a</sup>         | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 18                     | Q1 2021  | 0.8     | 18.0    | n.d.                 | 1.6                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 19                     | Q1 2021  | 0.6     | 12.8    | n.d.                 | >LOD<sup>a</sup>         | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 20                     | Q1 2021  | 0.6     | 10.8    | n.d.                 | >LOD<sup>a</sup>         | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 21                     | Q1 2021  | 0.5     | 11.6    | 0.1                  | 9.9                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 22                     | Q1 2021  | 0.8     | 16.9    | <LOQ                 | 9.1                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 23                     | Q1 2021  | 0.7     | 14.0    | n.d.                 | 1.0                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 24                     | Q2 2021  | <0.3    | 2.7     | n.d.                 | 3.4                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| 25                     | Q2 2021  | 1.0     | 18.5    | n.d.                 | 3.6                      | n.d.                 | n.d.                    | n.d.                       | n.d.                       | n.d.                       |
| Hashish sample | Period | THC (%) | CBD (%) | 5F-MDMB-PICA (μg/mg) | MDMB-4en-PINACA (μg/mg) | ADB-BUTINACA (μg/mg) |
|---------------|--------|---------|---------|----------------------|------------------------|----------------------|
| 1             | Q2 2020| 0.5     | 23.1    | 4.2                  | n.d.                   | n.d.                 |
| 2             | Q3 2020| 0.4     | 14.1    | n.d.                 | 7.2                    | n.d.                 |
| 3             | Q4 2020| -       | -       | n.d.                 | >LOD<sup>a</sup>        | n.d.                 |
| 4             | Q4 2020| 0.5     | 13.6    | n.d.                 | 3.4                    | n.d.                 |
| 5             | Q4 2020| 0.6     | 15.0    | n.d.                 | 1.7                    | n.d.                 |
| 6             | Q4 2020| 0.5     | 18.3    | n.d.                 | 6.5                    | n.d.                 |
| 7             | Q4 2020| 0.4     | 14.6    | n.d.                 | 6.7                    | n.d.                 |
| 8             | Q1 2021| 0.5     | 14.2    | n.d.                 | 6.7                    | n.d.                 |
| 9             | Q1 2021| 0.7     | 14.7    | n.d.                 | 6.1                    | n.d.                 |
| 10            | Q1 2021| 0.8     | 23.4    | n.d.                 | 6.7                    | n.d.                 |
| 11            | Q1 2021| 8.7     | 25.0    | n.d.                 | >LOD<sup>a</sup>        | n.d.                 |
| 12            | Q1 2021| 1.6     | 39.3    | n.d.                 | 6.2                    | n.d.                 |
| 13            | Q1 2021| 1.6     | 38.9    | n.d.                 | 6.1                    | n.d.                 |
| 14            | Q1 2021| 0.5     | 13.5    | n.d.                 | 3.7                    | n.d.                 |
| 15            | Q1 2021| 27.0    | 11.4    | n.d.                 | 3.0                    | n.d.                 |
| 16            | Q1 2021| 0.8     | 20.4    | n.d.                 | 6.5                    | n.d.                 |
| 17            | Q1 2021| 1.4     | 35.0    | n.d.                 | 5.8                    | n.d.                 |
| 18            | Q1 2021| 1.4     | 37.4    | n.d.                 | 5.8                    | n.d.                 |
| 19            | Q2 2021| 0.9     | 20.1    | n.d.                 | 7.7                    | n.d.                 |
| 20            | Q2 2021| 0.9     | 14.9    | n.d.                 | 7.0                    | n.d.                 |
| 21            | Q2 2021| 0.7     | 14.2    | n.d.                 | 5.0                    | n.d.                 |
| 22            | Q2 2021| 1.5     | 33.7    | n.d.                 | 6.8                    | n.d.                 |

Note: (A) Adulterated cannabis flowers and (B) adulterated hashish samples. “-” indicates samples, where insufficient material was available for phytocannabinoid quantification but tested positive with HRMS. “n.d.” stands for “not detected”. In bold: samples with similar MDMB-4en-PINACA content. 4F-MDMB-BINACA, 4F-MDMB-BICA, 5F-MDMB-PINACA, and 5F-MPHP-2201 were not detected in any hashish samples (Table B).

<sup>a</sup>Detected during initial screening, due to insufficient sample amounts not quantified.

<sup>b</sup>Seldomly detected, therefore not quantified.
Because of the high potency of many SCs, only small quantities of pure SCs are required to fabricate the final products, which then can be sold at standard market prices of drug-type cannabis.

The discussed advantages for producers and sellers of adulterated cannabis products are reduced, when hashish, instead of low-THC cannabis flowers, is used, particularly with regard to distribution of the final product. Hashish is illegal in Switzerland, regardless of its THC content. Nevertheless, as with the exception of two samples, which contained higher levels of THC (8.7% and 27% THC), the THC content of adulterated hashish samples was very low. The median THC content was 0.8% THC (range: 0.4–27.0%), with 66.7% of samples containing <1% THC. This indicates that the utilized raw material was very likely industrial-type cannabis. In the study by Oomen et al., six hashish samples, for which phytocannabinoid contents were available, showed low THC levels of <1%, therefore agreeing with our findings. While in the present study the number of adulterated hashish samples (47%) was nearly equal to the number of adulterated cannabis flowers (53%), this largely differed from the observations by Oomen et al. Of all adulterated samples, only 8.5% (n = 23) were hashish samples, the rest being comprised of cannabis flowers (73%, n = 197) or e-liquids (19%, n = 50). This could either indicate that adulterated hashish is less prominent in other regions or that adulterated hashish samples are less often handed for analysis and, therefore, underreported. Concerning the present study, the observed emerging use of hashish as carrier material might have been a reaction to the public and law enforcement being increasingly sensitized to the presence of adulterated cannabis flowers.

### Evaluation of self-reports

Self-reports were available whenever an individual had already consumed the respective product before handing a sample in. This was the case for 75% (n = 36) of samples containing SCs and for 66% (n = 31) of unadulterated samples. The reports belonging to two adulterated hashish samples, with elevated THC-levels (8.7% and 27%), were excluded, as they could not be exclusively assigned to one group. A list of the top five most frequent statements for the SC- and THC-group is shown in Table 2. For both groups the most often described experience was “exceptional strong effect.” This was described by 44% (n = 16) of the SC- and 29% (n = 9) of the THC-group, resulting in no statistical difference between groups (p = 0.21). However, “short effect duration” was described by 42% (n = 15) of the SC-group and was the second most reported observation for this group. This attribute was less often described for the THC-group (p = 0.013), as it was reported by 13% (n = 4) of the THC-group. Shorter effect durations of SCs, when compared with natural cannabis, have been previously reported in a study investigating reports of recreational drug users.

| SC-Group | n (%) |
|----------|-------|
| Exceptional strong effect | 16 (44) |
| Normal | 5 (16) |
| Headache | 5 (16) |
| Palpitations | 4 (13) |
| Dizziness | 4 (13) |
| Nausea | 4 (13) |
| Weak | 4 (13) |
| Short duration | 4 (13) |
| Strange taste | 4 (13) |

| THC-Group | n (%) |
|----------|-------|
| Exceptional strong effect | 9 (29) |
| Normal | 5 (16) |
| Headache | 5 (16) |
| Palpitations | 4 (13) |
| Dizziness | 4 (13) |
| Nausea | 4 (13) |
| Weak | 4 (13) |
| Short duration | 4 (13) |
| Strange taste | 4 (13) |
The statistical evaluation of adverse events and adverse effect subcategories is presented in Table 3. A higher likelihood \( (p = 0.041) \) for the occurrence of adverse events was shown for the SC-group when compared with the THC-group, as 75% \( (n = 27) \) of the reports from SC-group and 48% \( (n = 15) \) of the reports from the THC-group were classified to describe an adverse event. Neurologic effects, however, were shown to be independent of the consumed product \( (p = 0.31) \). The most prominent neurologic adverse effects in this study were headache for the THC-group \( (16\%, n = 5) \) and dizziness for the SC-group \( (14\%, n = 5) \).

Psychologic adverse effects were found to be more profound in the SC-group than the in THC-group \( (p = 0.0007) \). Severe psychologic adverse effects resulted in the admittance of two independent individuals of the SC-group to the emergency department. Both users reported strong psychologic adverse effects, including panic attacks and fear of death. A study comparing the clinical conditions of SCs and cannabis users found SCs to be associated with significantly more psychotic symptoms.\(^{61}\) Paranoia, hallucinations, and psychosis are symptoms frequently associated with SC intoxication.\(^{62-64}\)

In this study, SCs were additionally associated with a higher risk for cardiovascular adverse effects \( (p = 0.020) \). This is in accordance with existing literature on SCs as, ever since their emergence on the drug market, many SCs have been widely associated with cardiovascular adverse effects, including severe outcomes.\(^{5,29,63-68}\) The mechanisms behind the cardiac effects of SCs are still not completely understood.\(^{63}\) The often-observed higher activities of many SCs at CB1, when compared with THC, have been described as a contributing factor.\(^{67}\) However, other pathways may exist, as further toxicologically relevant receptors have not been thoroughly investigated.\(^{63}\) Toxicologically relevant pathways might be substance-dependent and not transferable to the whole class of SCs. Furthermore, CBD has been discussed to alter THC-effects.\(^{59}\) As the adulterated samples detected in this study contained CBD ranging from 2.7% up to 39.3%, a potential modulation of SC-effects cannot be excluded.

The herein presented adverse effects are largely in agreement with the reported adverse effects after consumption of adulterated cannabis products with MDMB-4en-PINACA reported by Oomen et al.\(^{22}\) The publication included a descriptive summary of reported adverse effects. Adverse effects stated by drug checking users comprised nausea, vomiting, paranoia, anxiety, hallucinations, tremors, paralysis, aggressiveness, insomnia, loss of consciousness, and palpitations. Information on the observed frequency of the stated adverse effects were not given. The authors reported on three individuals requiring emergency hospital treatment, due to adverse effects including excessive emesis, perspiration, panic attacks, tachycardia, amnesia, and seizures.

### Limitations

Concerning chemical analyses, potential degradation of natural cannabinoids and SCs cannot be ruled out, as some samples were stored for up to one and a half years before being subjected to semi-quantification. Three expected degradation products of detected SCs were screened (i.e., MDMB-4en-butanoic acid, 4F-MDMB-BICA-butanoic acid, and 5F-MDMB-PICA-butanoic acid). Results showed no detectable signals, thus implying little to no degradation of the corresponding SCs. A full validation for a quantitative method according to guidelines applied in forensic chemistry (e.g., SGRM) was omitted as a comparison of the content was still possible. Due to the limited sample material, samples were subjected to single measurements after being homogenized.

A limitation regarding the self-reported adverse effects was that medical confirmation (e.g., cardiovascular parameters and psychological screenings) of these symptoms were lacking. Also, dosages and co-ingestion of other relevant drugs were not accessible. Additionally, due to the study design involving volunteers using drug checking services, the study group was not randomized (e.g., age and gender). As people submitting cannabis samples at drug checking services often suspect sample adulteration when they experience unwanted or unexpected effects, this might have resulted in a preselection bias of the study group. Finally, the observed prevalence of adulterated products may not be representative for the whole drug market.
adulterated hashish samples, a relatively homogenous picture for MDMB-4en-PINACA was observed, while the results for cannabis flowers differed considerably.

Drug checking services enabled a unique insight into the drug market, as well as the timely detection of new developments surrounding NPS, as demonstrated in this study by the example of SCs. Thus, drug checking services, besides being an important harm-reduction tool in the sense of public health and prevention, offer the possibility to act as a market monitoring tool and further may give information on NPS, on which toxicological data are typically scarce. The data gained through drug checking services, whilst not validated or standardised, bear the potential to expand present knowledge gained through more established routes, as in, for example, case reports and case series after intoxication, helping to fill the gap between product and effects.

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DATA AVAILABILITY STATEMENT
The data that supports the findings of this study is available in the supplementary material of this article or available from the corresponding author upon reasonable request.

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