

# Comparison of Different Analytical Methods for the On-Site Analysis of Traces at Clandestine Drug Laboratories

René Reiss<sup>1</sup>, Frank Hauser<sup>2</sup>, Sven Ehlert<sup>1,\*</sup>, Michael Pütz<sup>2</sup> and Ralf Zimmermann<sup>1,3</sup>

<sup>1</sup> Joint Mass Spectrometry Centre, Chair of Analytical Chemistry, University of Rostock, Dr.-Lorenz-Weg 2, 18059 Rostock, Germany; rene.reiss@uni-rostock.de (R.R.); ralf.zimmermann@helmholtz-muenchen.de (R.Z.)

<sup>2</sup> Bundeskriminalamt-Federal Criminal Police Office (BKA), Forensic Science Institute, Äppelallee 45, 65203 Wiesbaden, Germany; frank.m.hauser@bka.bund.de (F.H.); puetzm@mail.uni-marburg.de (M.P.)

<sup>3</sup> Joint Mass Spectrometry Centre, Comprehensive Molecular Analytics, Helmholtz Zentrum München, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

\* Correspondence: sven.ehlert@uni-rostock.de; Tel.: +49-381-498-6532

**Abstract:** While fast and reliable analytical results are crucial for first responders to make adequate decisions, these can be difficult to establish, especially at large-scale clandestine laboratories. To overcome this issue, multiple techniques at different levels of complexity are available. In addition to the level of complexity their information value differs as well. Within this publication, a comparison between three techniques that can be applied for on-site analysis is performed. These techniques range from ones with a simple yes or no response to sophisticated ones that allow to receive complex information about a sample. The three evaluated techniques are immunoassay drug tests representing easy to handle and fast to explain systems, ion mobility spectrometry as state-of-the-art equipment that needs training and experience prior to use and ambient pressure laser desorption with the need for a highly skilled operator as possible future technique that is currently under development. In addition to the measurement of validation parameters, real case samples are investigated to obtain practically relevant information about the capabilities and limitations of these techniques for on-site operations. Results demonstrate that in general all techniques deliver valid results, but the bandwidth of information widely varies between the investigated techniques.

**Keywords:** amphetamine; methamphetamine; precursor; method comparison; on-site; clandestine laboratory



**Citation:** Reiss, R.; Hauser, F.; Ehlert, S.; Pütz, M.; Zimmermann, R.

Comparison of Different Analytical Methods for the On-Site Analysis of Traces at Clandestine Drug Laboratories. *Appl. Sci.* **2021**, *11*, 3754. <https://doi.org/10.3390/app11093754>

Academic Editor: Fabrizio Carta

Received: 24 February 2021

Accepted: 9 April 2021

Published: 21 April 2021

**Publisher's Note:** MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Copyright:** © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Drugs like amphetamine, methamphetamine, or 3,4-methylenedioxy-N-methamphetamine (MDMA) are known as amphetamine-type stimulants (ATS) [1]. Based on reported seizures, they are the most prevalent drugs after cannabis and cocaine in Europe [2]. Especially amphetamines and MDMA are predominantly found in northern and eastern Europe [2]. While most of the amphetamine production takes place in Belgium, the Netherlands, and Poland, methamphetamine is mainly produced in the Czech Republic [2]. For MDMA, the main production takes place in the Netherlands and Belgium [2]. The most common synthesis route for the illicit production of amphetamine is the Leuckart method [3]. The preferred production method of methamphetamine is the Nagai route and the production via Birch reduction [3]. While the usage of the Leuckart method for MDMA is known, most frequently the reductive amination with methylamine, hydrogen, and platinum dioxide catalyst is utilized [3]. Amphetamine is usually produced from the precursor phenylacetone (BMK or benzyl methyl ketone) [3]. In the case of methamphetamine, ephedrine and pseudoephedrine is a common choice [3]. For MDMA, piperonyl methyl ketone (PMK) is chosen frequently [3]. In order to circumvent the transport of scheduled precursor chemicals like BMK, producers started to utilize non-scheduled pre-precursors [2]. This is done, because most pre-precursors are not “scheduled” monitored. As the first step, a

pre-precursor is converted to the needed precursor that is afterwards applied to produce the drug itself. In recent years, one of the most relevant pre-precursors turned out to be alpha-phenylacetoacetonitrile (APAAN) [4]. APAAN is converted into BMK which is then utilized to produce amphetamine. These pre-precursors extend the possible compounds that can be found at clandestine laboratories. Therefore, interpretation of results is aggravated. This in turn, can imply the need for powerful analytical techniques in order to keep pace. In general, the investigation of clandestine laboratories is highly complex, since every laboratory has a unique setup. Examples of these differences can be different equipment to synthesise drugs, purities of chemicals and solvents, carefulness of the producers, and size and complexity of the laboratory itself and many more. Especially for amphetamine, large-scale productions are frequently observed which is supported by seizure data of amphetamine freebase in multiple countries, that originates from the Netherlands [4]. Due to this large-scale laboratory size, on-site assessment at clandestine laboratories becomes more difficult as the number of samples and their complexity, based on the diverse nature of the target compounds, increase as well. This applies particularly to inactive laboratories that are no longer in use and evidence of a former usage must be proven by taking samples from multiple surfaces. Another reason why trace analysis can be important, is to get quick information about worktops at laboratory storage sites if they are contaminated. This can be a necessary step of self-protection prior to crime scene investigations if highly potent and in non-visible amounts fully active drugs could be present. Some well-known techniques suitable for on-site analysis, are immunoassay drug tests (IDT) [5], tabletop nuclear magnetic resonance (NMR) spectroscopy [6], Raman spectroscopy [7], infrared (IR) spectroscopy [8], ion mobility spectrometry (IMS) [9], and mass spectrometry (MS) [10]. While IR, NMR and Raman spectroscopy are able to analyse known and unknown target compounds, their need for visible amounts of the target compound makes them unsuitable for trace analysis. Therefore, these techniques are not considered for the current evaluation and subsequent IDT, IMS and ambient pressure laser desorption hyphenated mass spectrometry (APLD-MS) are investigated. In addition, these techniques can be seen as representatives for other techniques of a similar complexity in each case. IDTs are fast to use, lightweight and straightforward. They are a well-established method and frequently used in laboratories, driver controls and can even be used by unskilled persons at workplaces [5]. Furthermore, they enable a fast, easy to use and affordable analysis for specific target compounds. In addition, the result interpretation is straightforward. Possible drawbacks are that mainly sum-parameters results are measured and a linear increase in cost and time if multiple samples should be analysed. IMS with thermal desorption represents portable state-of-the-art tools for surface analysis. It is an approved technique, which is applied for a long time, benefits from fast analysis time and is capable of detecting even traces of a target compound. Most relevant drawbacks are a low resolution, which leads to relative high false alert rates and easy overload which leads to time intensive cleaning [11]. Current research for on-site equipment is done in the field of direct desorption MS [9]. Within this field, the coupling of a desorption unit and an MS creates a system that combines benefits from both techniques. While a direct desorption allows for fast sample throughput, the MS enables the investigation of complex samples. For this coupling, multiple techniques are under investigation. In addition, some of these systems also allow to directly investigate suspicious surfaces. This further speeds up sample throughput and allow for spatially resolved surface investigations. The possibility to investigate only small areas of a given surface and bypass sampling swabs, also allows impression/mark preserving analysis to allow further investigations later on. This work focuses on the coupling of MS with laser desorption at ambient pressure, because no auxiliary media, such as gases or liquids, are needed and former research indicates the usefulness of this technique for such applications [removed due to journal double-blind policy] [12–14]. In addition, APLD-MS as the third technique for on-site detection, is seen as an example of a possible future technique that could be implemented for routine analysis and demonstrated promising results in this field of application. While all three techniques were examined for these target compounds,

literature lacks of direct comparisons of on-site samples and practical evaluation over different technology levels. Therefore, the aim of this publication is to compare IDT, IMS, and APLD-MS for trace analysis of amphetamine, methamphetamine and MDMA, intermediates, such as N-formylamphetamine (NFA) that are carried over to the main product [3], and drug precursors in clandestine laboratories. A benefit of these techniques is their easy on-site usability, compared to other techniques of their technology level. The limits of detection (LODs) were determined, real case scenario samples from former drug synthesis and seized clandestine laboratories are investigated. These samples demonstrate target analytes on complex matrices, resulting from on-site sampling. These real case scenarios aim to support the comparability of the investigated techniques on-site.

## 2. Materials and Methods

### 2.1. Chemicals

The following substances were obtained from the German Federal Criminal Police Office (BKA, Wiesbaden, Germany): 2-phenylacetoacetonitrile, amphetamine sulphate, ephedrine hydrochloride, amphetamine base, NFA, PMK, methamphetamine, MDMA hydrochloride, and amphetamine synthesis wastes. BMK was purchased from Sigma-Aldrich (St Louis, MO, USA). Caffeine was bought from Alfa Aesar (Karlsruhe, Germany). All analytes were dissolved in methanol from Carl Roth GmbH + Co. KG (Karlsruhe, Germany). Methane 4.5 as chemical ionisation (CI) reactant gas for MS and helium 5.0 were bought from Linde AG (Berlin, Germany).

### 2.2. Sampling Swabs

Sampling swabs are used for all measurements except for the LOD determination with ITDs. For all measurements Nomex (meta-aramid) sampling swabs from Smiths Detection Inc. (Wiesbaden, Germany) were used as sample tool. Wall sampling was done manually.

### 2.3. Immunoassay Drug Test

The applied IDTs are called “Drugwipe 2” from Securetec Detektions-Systeme AG (Brunnthal, Germany). Tests were conducted according to the producer’s instruction. LODs were determined by placing 1 µL of analyte at the sampling surface of the IDT. For practical samples, the IDT was wiped over the surface according to the producer’s instruction. Results were interpreted optically under daylight. The result were interpreted by two scientists individually.

### 2.4. Ion Mobility Spectrometry

The IMS measurements were conducted with an Ionscan 500 DT version 3.05.031, build by Smiths Detection Inc. (Wiesbaden, Germany). Version of the operating system is 6.0. Applied parameters are a drift tube flow of 300 mL/min, a desorber temperature of 245 °C, a positive drift tube voltage of 1577 V and ambient pressure of 1020 hPa. Sampling was done in positive mode, according to the recommendation of the manufacturer. Therefore, the sampling swab was inserted in the IMS and the measurement was started via software. This was done for LOD determination and practical sample measurement. For all samples, the cleanliness of the IMS was tested prior to a measurement with a clean sample swab. If contaminations from previous measurements were detected, the device was cleaned and tested again.

### 2.5. Ambient Pressure Laser Desorption—Mass Spectrometry

A 445 nm laser diode NDB7875 from Nichia (Tokushima, Japan) was applied for desorption with a surface power input of 0.98 W. The laser was operated in continuous wave (CW) mode. Mass spectra were acquired utilizing a Varian Inc. (Walnut Creek, CA, USA) ion trap 240-MS. Laser light is transferred from the laser to the ambient pressure desorption head with a 1250 µm Optran UV laser fibre from CeramOptec GmbH (Bonn, Germany). The ambient pressure desorption head was self-build and made out of brass

and polytetrafluoroethylene for thermal separation. A detailed schematic of the APLD and its parts is available in a previous publication [12].

The procedure to analyse a sample, was to place a sample (swab) in front of the APLD unit and activate the laser while the MS is active. The APLD system was heated to 200 °C with a flow rate of 3 mL/min helium. All compounds were analysed with positive polarity mode. Methane as reactant gas is used for chemical ionisation generating primarily protonated quasi molecular ions. For practical sample measurement, settings are the same as for LOD measurements.

#### 2.6. Determination of Limits of Detection + Sampling of Real Case Samples

For LOD determination, one microlitre of a diluted analyte solution was dropped on a sampling swab surface to prepare a sample. The pure substance was diluted with methanol to the needed concentration. After the solvent evaporated, the residue carrying surface was analysed.

For the real case samples, sampling swabs were wiped three times over the suspicious surface with a sampling length of about 0.1 m each. Sampling swabs were prepared for every technique and stored afterwards, sealed in plastic bags, inside a refrigerator until analysis.

### 3. Results and Discussion

#### 3.1. Method Comparison

One major parameter for a comparison is the possibility to detect target compounds. For the investigated target compounds there is a clear trend for the three investigated methods. IDTs are only capable of detecting compounds that they are specifically made for. In this case, amphetamine, methamphetamine, and MDMA. Compared to IDTs, IMS systems are more flexible and allow to detect a broader range of analytes. The ability to ionise target compounds is the main limitation for IMS systems, valid for, e.g., BMK. In this study, all target compounds had been detected successfully with APLD-MS. Like IMS, MS is limited to analytes that can be ionised. Due to the utilized chemical ionisation method, this technique is capable to analyse a wide variety of substances. This leads to the observation, that the APLD-MS can detect the highest number of compounds.

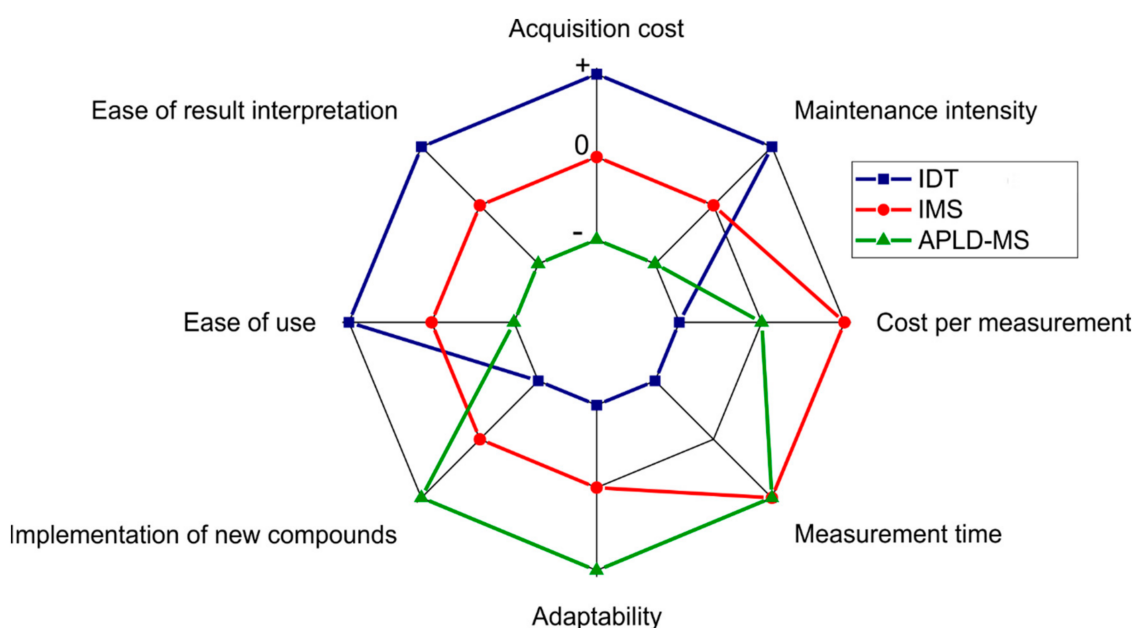
The parameter selectivity is of interest as well as it influences the possible field of application. While IDTs are made to investigate if a number of target compounds are present, no information can be gathered on what specific substance triggered a positive signal. In addition, every new target compound that should be investigated needs a new IDT. In theory, IMS is capable to distinguish different possible substances. Practically, the low resolution of most IMS makes it difficult to distinguish between similar compounds and for the same reason, the presence of multiple substances can be an issue, too. In contrast to IDTs, IMS libraries can be updated to detect new target compounds. The most selective system in this study, even for multiple substances present, is the APLD-MS. It allows identifying target compounds and even unknown substances can be presumed, based on the mass spectra.

Another major parameter is the complexity of the analytical technique and its user requirements. IDTs are very compact, cheap, easy to handle and require only knowledge about possible cross-reactions and contraindications. IMS in comparison, needs significant set-up time previous to a measurement, is considerably larger, orders of magnitude more expensive in acquisition, and needs trained personal for operation. In addition, many IMS utilise a Ni63-source and thus may require radiation protection trained personal. As many on-site measurements were done for target compounds that can be found in a system-integrated library, result interpretation is done by the device, and hence no additional training is needed for the operator. APLD-MS needs a well-trained operator, electricity and pressurised gases. Its set-up time is higher compared to IMS and the operator's knowledge needs to be the highest of all three methods. The operators training is needed

for performing measurements as well as interpreting obtained results. Therefore, APLD-MS is the most sophisticated system that was investigated.

In addition to the above discussed set-up time, duration per measurement, as another parameter, is especially relevant for larger operations and time critical activities. According to the conducted experiments, the highest sample throughput is achievable for IMS. It took about eight seconds to perform one measurement. APLD-MS needed about 30–60 s to obtain results. The longest time was necessary for the IDT. About three minutes passed before the enzymatic reaction was concluded. Depending on the sample number and available staff, parallel testing could decrease this time to a certain extent and change the necessary total time. These results imply, that the sample amount was adequate and no overload occurred. This overload is imaginable for real samples with unknown concentration, especially at on-site measurements. This additional cleaning affects only IMS and APLD-MS because IDTs are only used once. In addition, the possibility of IDTs to analyse two or more drugs at once should be mentioned as well.

All mentioned aspects can be transformed into eight key parameters that can be compared for the investigated techniques. These parameters are cost per measurement, acquisition cost, ease of use, ease of interpretation, possibility to implement new compounds, adaptability to sample shapes and types, measurement time and need for maintenance. Figure 1 illustrates this comparison in a graphical way. It exhibits that each technique has its strengths and weaknesses and that there is not a single technique that is suitable for all applications.



**Figure 1.** Visualisation of key parameters for the comparison of all three methods. Plus means positive or better, zero means neutral or in between, and minus means negative or worse, in comparison to the other techniques.

If only a few samples should be analysed for amphetamine, methamphetamine, or MDMA, IDTs could be the method of choice. In case that routine measurements are needed and the target compounds are limited to known compounds of a drug production, the use of IMS could be the method of choice. Assuming that complex samples need to be investigated, APLD-MS or another ambient MS technique can demonstrate its strengths.

### 3.1.1. Limits of Detection

#### IDT

The investigated IDTs are designed to detect amphetamine, methamphetamine, and MDMA. Therefore, IDTs are a suitable example to examine the chosen target compounds. The information gathered from a measurement is that one of the investigated substances is present or not. No statement is made what specific target compound is found if a positive result is obtained. To gain further information about the capabilities of IDTs, the LOD was determined for amphetamine, methamphetamine and MDMA separately. The results of Table 1 reveal that clear visible indication/bar is possible down to 2 ng total target compound. In some cases, lower substance amounts down to 1 ng resulted in positive signals (slightly visible bar) as well, but were discarded due to the inconsistency of the results. In addition, all three substances yielded the same LOD. This is interesting because in most cases of on-site analysis this test only informs about a sum parameter. The knowledge that all investigated compounds can be detected, at a similar amount, eases the practical use for first responders. Cross-reactions were tested with all listed drug precursors and caffeine. No false positive results were obtained up to the investigated limit of one thousand times the LOD (2000 ng) per substance.

**Table 1.** Total LOD of all investigated substances for all investigated methods. Two bars mean no LOD determinable.

Substance Name	LOD IDT/ng	LOD IMS/ng	LOD APLD-MS/ng
Amphetamine base	2	2	20
Amphetamine sulphate	2	2	10
MDMA HCl	2	5	21
Methamphetamine	2	1	11
APAAN	–	5	10
Ephedrine HCl	–	1	6
NFA	–	9	9
BMK	–	–	11
PMK	–	–	6

#### IMS

The chosen IMS is mobile and needs only electricity for operation. Therefore, it is suitable for on-site analysis of suspicious surfaces. To achieve practically relevant LODs, Table 1 shows the lowest total amount of substance that was necessary to trigger an alert. The alert itself was triggered for signal-to-noise ratios of  $S/N \geq 10$  to avoid noise based errors. This procedure was chosen, because most first responders are no analytical chemists and cannot interpret raw plasmagram data. LODs in the low nanogram range were obtained for all drugs and most drug precursors. Only BMK and PMK gave no response at all. For amphetamine, it was investigated if the salt form, and therefore physical properties like vapour pressure, has an influence on the LOD. As Table 1 reveals, no such behaviour was observed. Therefore, the salt form seems to have negligible influence on the detectability by IMS.

#### APLD-MS

The MS does not have a specific trigger or detection alert for detected compounds, because it is a normal laboratory device. Therefore, the LODs are defined by a signal-to-noise ratio  $S/N$  of three. To obtain comparable results, the signal intensity was not extrapolated to a  $S/N$  of three; instead, the LOD represents the lowest total amount of substance that was actually measured. The APLD was capable of detecting all investigated target compounds and the achieved LODs for all substances are in the same order of magnitude, ranging from 6 ng for PMK to 21 ng for MDMA HCl.

If, in summary, the LOD is compared between all investigated techniques, no major variations are observed. While IDTs reveal the best overall LODs with 2 ng for all substances, IMS results are slightly higher and deviate between 1 ng for methamphetamine and 9 ng for NFA. In the utilised setup, APLD-MS obtained 2 ng to 21 ng and therefore about two to ten times higher LODs, compared to IDTs.

### 3.2. Analysis of Real Samples

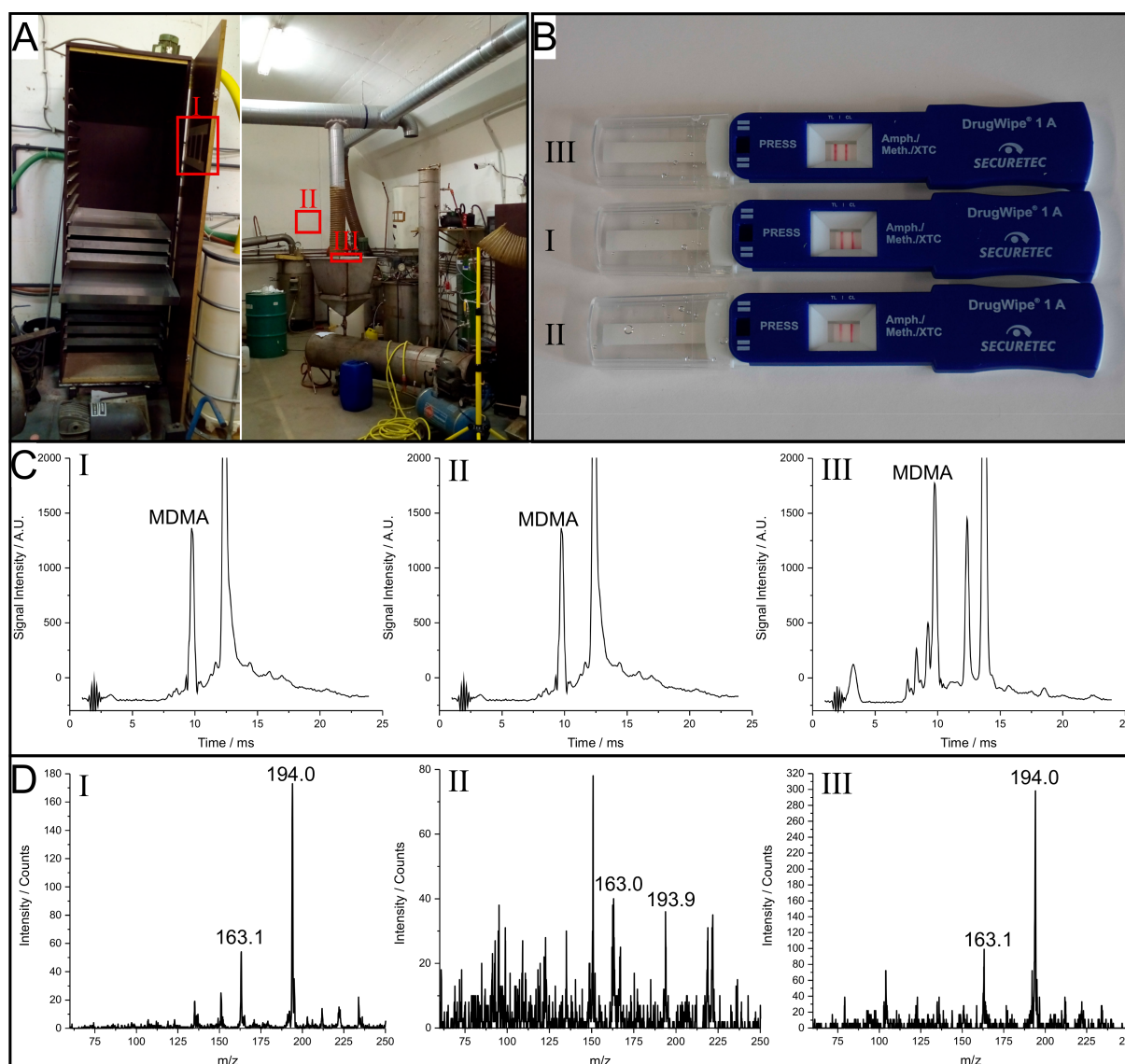
#### 3.2.1. Samples from a Former MDMA Lab

To gain information about the capabilities of the tested techniques under real conditions, practical measurements were performed at a former clandestine MDMA laboratory. The clandestine laboratory and parts of the utilised equipment can be seen in Figure 2. Three different samples were acquired and analysed. In addition to two spots from an actively used Büchner funnel and drying cabinet, one sample was obtained from the wall behind the equipment. This sample is particularly interesting because the laboratory was equipped with professional equipment allowing a less MDMA contaminating work flow during production, compared to amateur productions. In Figure 2A, all sample spots, in the clandestine laboratory, are marked with red rectangles. Visual results of the IDT are shown in Figure 2B. While the drying cabinet and the Büchner funnel exhibit similar colour intensities, a lower colour intensity, and therefore lower concentration of MDMA was found for the wall sample. Detection results of MDMA for IMS are plotted in Figure 2C. Therein, the peak at around 9.8 ms is related to MDMA and exhibit similar concentrations for the wall sample and the drying cabinet. A higher concentration of MDMA was found for the Büchner funnel. This discrepancy can be explained due to local variations in concentration at the surface of the drying cabinet and funnel. These variations are most likely based on the use of multiple sample swabs, applied to areas close together, which were necessary for the applied test procedure. In Figure 2D, the positive CI mass spectra of the investigated surfaces are plotted. The measured concentration are in good agreement with the IDT results. The highest concentration of MDMA was found for the Büchner funnel, followed by the drying cabinet. The lowest concentration observed correlates to the wall sample.

Table 2 summaries the results for the investigation of sample swabs from all three areas for the three investigated techniques. The measured concentration differs for IMS and APLD-MS. Observed signal differences could be based on sampling variations, such as pressure applied to the sample swab or sampled area, MDMA surface concentration inhomogeneity or differences in sample transfer efficiency between pad and investigated surface. While the concentration of MDMA differs between the sample spots, positive detection was possible for all samples with all investigated methods. Therefore, the LOD of all techniques seems to be sufficient for this practical scenario. No amounts or concentrations of the tested sample are given, as not all techniques enables access to this information.

**Table 2.** Sampling swabs applied at different spots of a clandestine MDMA laboratory. All sampling swabs are examined for MDMA. Plus means positive detection.

Sample	IDT	IMS	APLD-MS
Drying cabinet	+	+	+
Büchner funnel	+	+	+
Wall	+	+	+



**Figure 2.** (A) Sampled areas are (left to right): drying cabinet, wall and Büchner funnel, all marked with red rectangles. (B) Positive IDTs of the sample areas (indicated by two bars) at (A). Results are (from up to down): Büchner funnel, drying cabinet and wall. (C) IMS measurements of the three sampling spots. IMS plasmagrams are in the following order (left to right): drying cabinet, wall, and Büchner funnel. MDMA signal at around 9.8 ms. (D) Positive CI mass spectra of the three sampling spots. Spectra are in the following order (left to right): drying cabinet, wall, and Büchner funnel. The signal of 194 m/z is related to the molecular ion peak  $[M + H]$  and 163 m/z corresponds to  $[M - HN - CH_3]$ .

### 3.2.2. Amphetamine Samples from Contaminated Glassware

Further practical measurement experience was gained, by analysing residues on equipment of an amphetamine synthesis. For this investigation the Leuckart method for synthesising amphetamine was chosen. This was done by a four-step reaction [15–17]. The first step was the conversion of APAAN into BMK with concentrated sulphuric acid and water. The generated, BMK containing, organic phase was afterwards mixed with formamide and formic acid, without purification (Leuckart step 1). The thereby generated, NFA containing, organic phase was once more utilised without further purification, and mixed with concentrated hydrochloric acid and neutralised after the reaction was finished (Leuckart step 2). The last step was the precipitation of amphetamine sulphate with the aid of sulphuric acid. In addition to both Leuckart step residues and accrued aqueous waste was investigated. For all three samples, the pre-precursor APAAN, the precursor



BMK, the intermediate NFA and the product amphetamine were investigated. Table 3 summarises all observed results. For the first Leuckart step, only NFA was detected positively with IMS and APLD-MS. The other substances gave no signal, either due to low abundance or because the technique is not suitable to analyse them. For the second Leuckart step, all three techniques were able to detect amphetamine. Additional traces of NFA were only detected with APLD-MS. Analysis of the aqueous waste resulted in positive detection of amphetamine for all three techniques. In comparison to this, BMK was found with APLD-MS only. While synthesis waste can be commonly found at clandestine laboratories, the executed measurements indicate that they can be difficult to analyse on-site. The observed difficulties could be related to the complexity of the mixtures and the concentration differences of the analytes. Overall, IDTs were able to correctly detect amphetamine regarding the laboratory analysis results. IMS was able to detect amphetamine and in addition, NFA at Leuckart step one. Most analytes were detected with APLD-MS, the observed analytes are amphetamine, NFA, and BMK. Therefore, these practical measurements indicate similar findings as the practical samples from Section 3.2.1. Within the limitations of a technique, all techniques deliver useful information for the presence of target compounds. In addition, the more complex and sophisticated a setup is, the more information can be obtained.

**Table 3.** Sampling swabs applied at different glassware of an amphetamine. ND mean technically not detectable, plus means positive detection and minus means negative detection. All samples were measured once, due to limited samples.

Sample	IDT	IMS	APLD-MS
Aqueous waste Leuckart step 1			
APAAN	ND	–	–
BMK	ND	ND	–
NFA	ND	+	+
Amphetamine	–	–	–
Aqueous waste Leuckart step 2			
APAAN	ND	–	–
BMK	ND	ND	–
NFA	ND	+	+
Amphetamine	+	+	+
Aqueous waste Steam distillation			
APAAN	ND	–	–
BMK	ND	ND	+
NFA	ND	–	–
Amphetamine	+	+	+

#### 4. Conclusions

This publication centres on forensic applications of three analytical techniques and the informational content that can be gained with them. The techniques, compared for the investigation of target compound traces at clandestine laboratories are IDT, IMS, and APLD-MS. These three techniques represent different approaches for the on-site analysis of target compounds. To enable better comparability, real samples were collected from contaminated surfaces of a clandestine MDMA and amphetamine-contaminated glassware. Measurements of these crime scene scenarios revealed that all techniques were able to detect MDMA on different collected sampling swabs, collected across the clandestine laboratory. Samples from contaminated glassware are analysed for the presence of amphetamine itself, the intermediate NFA and the precursors APAAN and BMK. While, like for MDMA, all techniques were able to detect amphetamine, only IMS and APLD-MS were able to detect the intermediate and only APLD achieved to detect BMK as a drug precursor.

In conclusion, the direct comparison for the same samples reveal that the preferred technique depends on the analytical capabilities needed for a certain issue as more analyti-

cal flexibility and explanatory power is correlated to higher sophisticated techniques. IDTs are inexpensive and can be handled properly after a short briefing. The major drawback is the limitation to specific target compounds. IMS is capable of analysing multiple target compounds and more cost-effective if many samples should be analysed. Drawbacks are the higher device acquisition costs and the need for a trained operator. Ambient MS is capable of analysing a wide variety of target compounds, even simultaneously. Especially the proven extension of the capability to detect forensically relevant precursor compounds allows a more distinct statement of the used reaction pathways, and moreover to identify potential sources of the utilised precursors. To achieve these benefits, high expenses and a highly trained operator are necessary. While all techniques were able to fulfil the basic needs of first responders for on-site investigations, only an increasing system complexity allows to gain information for in-deep analysis of a specific forensic or scientific question.

**Author Contributions:** R.R. and F.H. conceived and designed the experiments; R.R. and F.H. performed the experiments; R.R. analysed the data; M.P. and R.Z. contributed reagents, samples, measurement tools, and expert knowledge for those; R.R. wrote the paper; S.E., M.P., and R.Z. contributed significantly to the discussion and revision. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research was funded by the Federal Office of Civil Protection and Disaster Assistance of Germany (grant number FP406 “SEMFreS”).

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to federal safety regulations.

**Acknowledgments:** This work was supported by the Federal Ministry of the Interior (BMI) and the Federal Office of Civil Protection and Disaster Assistance of Germany.

**Conflicts of Interest:** The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

## References

1. United Nations Office on Drugs and Crime. *World Drug Report 2020*; United Nations: Vienna, Austria, 2020.
2. European Monitoring Centre for Drugs and Drug Addiction and Europol. *European Drug Report 2020; Trends and Developments*, Publications Office of the European Union: Luxembourg, 2020.
3. United Nations Office on Drugs and Crime. *Recommended Methods for the Identification and Analysis of Amphetamine, Methamphetamine and Their Ring-Substituted Analogues in Seized Materials*; United Nations: Vienna, Austria, 2006.
4. European Monitoring Centre for Drugs and Drug Addiction and Europol. *EU Drug Markets Report: In-depth Analysis*; Publications Office of the European Union: Luxembourg, 2016.
5. De Giovanni, N.; Fucci, N. The Current Status of Sweat Testing For Drugs of Abuse: A Review. *Curr. Med. Chem.* **2013**, *20*, 545–561. [[CrossRef](#)] [[PubMed](#)]
6. Zhong, Y.; Huang, K.; Luo, Q.; Yao, S.; Liu, X.; Yang, N.; Lin, C.; Luo, X. The Application of a Desktop NMR Spectrometer in Drug Analysis. *Int. J. Anal. Chem.* **2018**, *2018*, 3104569. [[CrossRef](#)]
7. Gerace, E.; Seganti, F.; Luciano, C.; Lombardo, T.; di Corcia, D.; Teifel, H.; Vincenti, M.; Salomone, A. On-site identification of psychoactive drugs by portable Raman spectroscopy during drug-checking service in electronic music events. *Drug Alcohol Rev.* **2019**, *38*, 50–56. [[CrossRef](#)] [[PubMed](#)]
8. Tsujikawa, K.; Yamamuro, T.; Kuwayama, K.; Kanamori, T.; Iwata, Y.T.; Miyamoto, K.; Kasuya, F.; Inoue, H. Development of a Library Search-Based Screening System for 3,4-Methylenedioxyamphetamine in Ecstasy Tablets Using a Portable Near-Infrared Spectrometer. *J. Forensic Sci.* **2016**, *61*, 1208–1214. [[CrossRef](#)] [[PubMed](#)]
9. Sisco, E.; Verkouteren, J.; Staymates, J.; Lawrence, J. Rapid detection of fentanyl, fentanyl analogues, and opioids for on-site or laboratory based drug seizure screening using thermal desorption DART-MS and ion mobility spectrometry. *Forensic Chem.* **2017**, *4*, 108–115. [[CrossRef](#)] [[PubMed](#)]
10. Forbes, T.P.; Staymates, M.; Sisco, E. Broad spectrum infrared thermal desorption of wipe-based explosive and narcotic samples for trace mass spectrometric detection. *Analyst* **2017**, *142*, 3002–3010. [[CrossRef](#)] [[PubMed](#)]

11. Seto, Y.; Kanamori-Kataoka, M.; Tsuge, K.; Ohsawa, I.; Matsushita, K.; Sekiguchi, H.; Itoi, T.; Iura, K.; Sano, Y.; Yamashiro, S. Sensing technology for chemical-warfare agents and its evaluation using authentic agents. *Sens. Actuators B Chem.* **2005**, *108*, 193–197. [[CrossRef](#)]
12. Reiss, R.; Ehlert, S.; Heide, J.; Pütz, M.; Forster, T.; Zimmermann, R. Ambient Pressure Laser Desorption—Chemical Ionization Mass Spectrometry for Fast and Reliable Detection of Explosives, Drugs, and Their Precursors. *Appl. Sci.* **2018**, *8*, 933. [[CrossRef](#)]
13. Ehlert, S.; Hölzer, J.; Rittgen, J.; Pütz, M.; Schulte-Ladbeck, R.; Zimmermann, R. Rapid on-site detection of explosives on surfaces by ambient pressure laser desorption and direct inlet single photon ionization or chemical ionization mass spectrometry. *Anal. Bioanal. Chem.* **2013**, *405*, 6979–6993. [[CrossRef](#)] [[PubMed](#)]
14. Ehlert, S.; Walte, A.; Zimmermann, R. Ambient pressure laser desorption and laser-induced acoustic desorption ion mobility spectrometry detection of explosives. *Anal. Chem.* **2013**, *85*, 11047–11053. [[CrossRef](#)] [[PubMed](#)]
15. Power, J.D.; Barry, M.G.; Scott, K.R.; Kavanagh, P.V. An unusual presentation of a customs importation seizure containing amphetamine, possibly synthesized by the APAAN-P2P-Leuckart route. *Forensic Sci. Int.* **2014**, *234*, e10–e13. [[CrossRef](#)] [[PubMed](#)]
16. Crossley, F.S.; Moore, M.L. Studies on the leuckart reaction. *J. Org. Chem.* **1944**, *9*, 529–536. [[CrossRef](#)]
17. Hauser, F.M.; Rößler, T.; Hulshof, J.W.; Weigel, D.; Zimmermann, R.; Pütz, M. Identification of specific markers for amphetamine synthesised from the pre-precursor APAAN following the Leuckart route and retrospective search for APAAN markers in profiling databases from Germany and the Netherlands. *Drug Test. Anal.* **2018**, *10*, 671–680. [[CrossRef](#)] [[PubMed](#)]