



## Customer Insights

- LC-MS for Toxicology: Pushing the Limits of Speed and Sensitivity in Drug Screening

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# LC-MS for Toxicology: Pushing the Limits of Speed and Sensitivity in Drug Screening

Ground-breaking LC-MS solutions enable general unknown analysis of drugs in biological samples, at the specialized laboratory of Dr. Michael Böttcher, MVZ Labor-Dessau GmbH



Dr. Michael Böttcher's specialist medical laboratory uses cutting-edge toxicological instrumentation to offer screening services for clinics and organizations across Europe.

*"We rely on Bruker's robust LC-MS/MS solution, the Toxtyper™, to rapidly analyze biological samples for drugs and drugs of abuse, with unprecedented accuracy."*

## The Medizinisches Versorgungszentrum (MVZ) Labor Dessau GmbH, Limbach Group

The MVZ Laboratory based in Dessau, Germany, is renowned for its specialist capabilities in drug screening analysis and toxicological studies, and offers a complete analysis spectrum for a wide range of biological matrices. The MVZ Laboratory Dessau, which is divided into three departments: Department of Toxicology, Department of Microbiology and Molecular Biology and the Department of Clinical Chemistry, is part of the wider Limbach Group of over 5,000 working members. The Department of Toxicology is run by Dr. Michael Böttcher, and the MVZ Laboratory Dessau has a total of 250 employees, of which 25 are employed within the Department of Toxicology.

Dr. Böttcher is the head of Drugs and Drugs Analysis in the Limbach Group, and leads his laboratory in their drug analysis service. He is responsible for ensuring the laboratory's methods are constantly under development to remain relevant in the evolving drugs market, and has been leading this work for the past 17 years. As a medical laboratory, the work spans microbiology and molecular biology, as well as clinical chemistry. The MVZ Laboratory Dessau is the largest in Germany for drug testing, and the Limbach Group as a whole is one of the largest of its kind in Europe.

As a comprehensive analytical facility, the laboratory receives samples from a vast range of sources: *"At Lab-Dessau we do all kinds of drug testing: therapeutic drug monitoring, drugs of abuse testing, workplace drug testing, intoxication cases, clinical drugs testing, especially for addiction medicine. We work for a large number of addiction clinics in large cities like Berlin. We monitor therapeutic drugs in addition to looking for drugs of abuse"* explains Dr. Böttcher, *"we work for many institutions which are involved with addiction or drugs of abuse."* This includes occupational health clinics, psychiatric hospitals, prisons, specialist psychiatric prisons, as well as private physicians who are working with addicts, for example in methadone programs.

*"We are very specialized in numerous rare drugs tests. We also conduct forensic testing – as we're forensic accredited we work for a number of Forensic Institutes. A lot of customers need new psychoactive substance testing which is less routine, so they send the samples to us because of our renowned specialist capabilities,"* comments Dr. Böttcher. Samples are sent to the laboratory frequently for synthetic cannabinoid testing, as well as synthetic opioids and internet drugs, so called 'legal highs'. Modern 'designer drugs' are sent to the laboratory, in addition to those which have been on the market for decades. Dr. Böttcher's laboratory is capable of analyzing drugs from capillary blood samples, urine, hair, and oral fluid – the latter of which has been most recently optimized and is particularly unique to this laboratory, as Dr. Böttcher explains:

*"We are quite specialized in oral fluid testing. We receive and test approximately 300-400 oral fluid samples per day and unlike many other laboratories which use immunoassay techniques, we use liquid chromatography-tandem mass spectrometry (LC-MS/MS). Using this method, we routinely look for 68 substances in one run, which is done very sensitively. From the beginning this has been a highly sophisticated testing method."*

The laboratory relies on dependable instruments which operate with minimal downtime, in order to service customers with time-sensitive samples. The ability to run general unknown analysis – a broad screening method which screens for over 4000 substances – depends on the comprehensive library of drug compounds available to the laboratory, so maintaining this as well as updating methods is critical to ongoing research and service development.

## Collaboration

Gas chromatography mass spectrometry (GC-MS) is the traditional approach to toxicological drug screening using general unknown analysis, but has steadily been overshadowed by the rapid turnaround time, ease of use and high sensitivity of innovative LC-MS methods. Dr. Böttcher's laboratory still uses GC-MS for screening certain samples, as some substances are not visible using LC-MS, but for routine work the laboratory now uses the Toxtyper™ - an LC-MSn library-based solution from Bruker Daltonics – which is described by Dr. Böttcher as a better way to handle samples and satisfy customers.

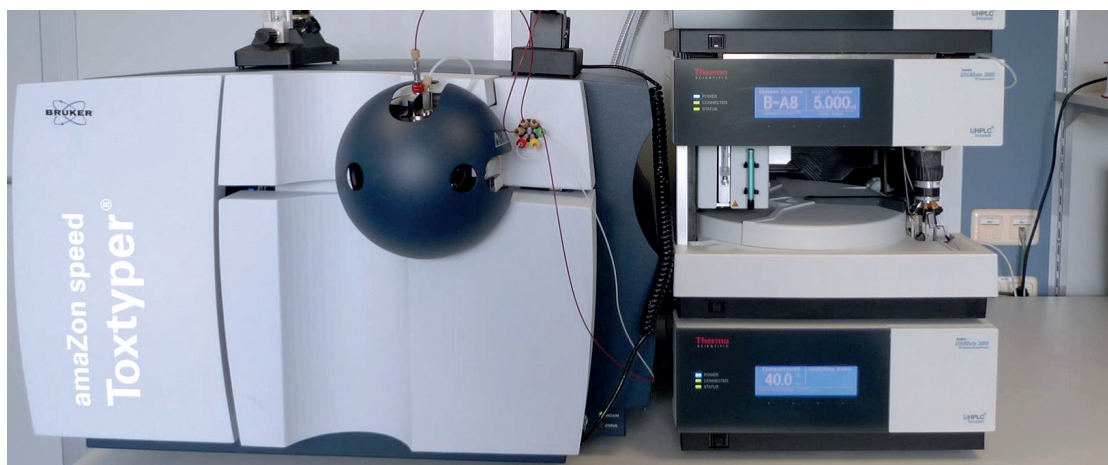
The unique collaboration between Bruker and the laboratory is based on the superior performance of the Toxtyper™ and the associated library. Dr. Böttcher describes the nature of the relationship:

*"We visited Bruker at a conference booth, which spurred an interest in the Toxtyper™: it was clear it was superior to GC-MS. We then visited Bruker headquarters in Bremen two or three times to analyze some samples, as well as sending them from Dessau."*

*"We were extremely impressed with the sensitivity, ease of use and rapid sample preparation."*

*"Bearing in mind we didn't have any peer recommendations to base our decision on – because at this stage we were among the first to do this – the decision was an easy one, there was no comparison to be made and no question that we should use this instrument."*

Before purchasing the Toxtyper™, general unknown analysis using GC-MS on oral fluid was not cost-effective, and therefore not offered to customers. If customers are unaware that a certain type of screening is possible, they will not generate demand for it. The introduction of the Toxtyper™ allowed the laboratory to lower the cost of general unknown analysis, and therefore offer this service. To herald this, last year at the German Addiction



Medicine Conference, the group’s presentation won first prize – an unusual accomplishment for a laboratory topic in addiction medicine. *“They were convinced that this was a very nice approach, because with one shot you can see so many substances”* comments Dr. Böttcher.

Dr. Böttcher’s laboratory services customers all over Europe, including in Ireland, the Netherlands, Sweden, Poland and Austria, and are renowned for their unique routine capabilities and rapid turnaround time.

## Unique Techniques

For general unknown analysis on blood, oral fluid and urine, Dr. Böttcher’s laboratory uses the Toxytyper™, which is easily customized to the needs of the laboratory and its customers. Previously, it was not possible to conduct broad analysis on oral fluid samples, but since purchasing the Toxytyper™ three years ago, this has been added to the laboratory’s repertoire of services.

Alternatively, where the most important drugs are anticipated, multi-target analysis is conducted and embedded in the laboratory’s multi-target analytical system with LC-MS/MS. This can be modified and adapted to the customer’s individual needs, and currently holds the capability to screen for 68 different substances. The laboratory’s dedicated multi-target methods, for example an opiate method or a benzodiazepine method, are comprehensive for that specific substance class.

*“The customer usually decides when we conduct multi-target analysis or general unknown analysis, but this can depend on the case. For example, if a certain case cannot be solved using one dedicated analysis, general unknown analysis is implemented. But if a customer requests an opioid test, we would use the dedicated opioid method. For the opioid method we can test for over 60 substances, the benzodiazepine method, 50 substances and with the synthetic cannabinoid method we can test for approximately 100 substances. This can be applied to oral fluid, but also other body fluids”* comments Dr. Böttcher.

The laboratory has experienced exponential growth in their turnover of biological sample analysis and following the successful output of the Toxytyper™, a second instrument was purchased. Dr. Böttcher elaborates:

*“We had more samples than the first Toxytyper™ could handle. We were quite successful with this idea and the turnaround time was increased, so we bought a second instrument to further our method development. For routine general unknown analysis, we don’t use GC-MS anymore but in some cases, particularly in post-mortems where the matrix may be contaminated, it is still a useful backup technique. Post-mortems produce a lot of ion suppression in LC-MS, and the results are less honest than GC-MS results. The Toxytyper™ is a better way to handle the samples and get more satisfied customers – our customers have learned that we’re quicker now, and have more sensitive techniques for most substances.”*

	General unknown analysis (Untargeted analysis) (Toxytyper™)	Multi-target screening (LC-MS/MS)
Number of substances	4000	68
Sample types	Oral fluid, urine, blood	Oral fluid, urine, hair, blood, vitreous humor, meconium
Dedicated methods		Opiates/opioids = 65 substances Benzodiazepines = 50 substances Synthetic cannabinoids = 100 substances Amphetamines/designer drugs = 70 substances
Sensitivity	1-25 ng/ml	0.1-2 ng/ml (10 x more sensitive)

Table 1: LC-MS drug screening capabilities at the MVZ Laboratory Dessau, Limbach Group.

## Takeover of the Toxyter™

Prior to their collaboration with Bruker, Dr. Böttcher's laboratory used GC-MS for general unknown drug analysis. This method is still in use and has advantages in certain circumstances, but the Toxyter™ provides superior analytical capacity and has a number of advantages, such as: high sensitivity, ease of training, simple data evaluation, near 24/7 running time and most importantly, extremely rapid sample preparation time. Dr. Böttcher explains why this is such a benefit:

*"With GC-MS, you have to complete three sample preparation steps – hydrolysis, extraction and derivatization – before you can run the samples, all of which are very time consuming. All these steps are very selective and this is why we have a loss of substances. The samples must be run in batches as sample prep is so cumbersome, so if an urgent sample arrives late it is uneconomical to add to the routine. This is disadvantageous for general unknown analysis, as you don't know what you are searching for in the first place. As an LC system, the Toxyter™ doesn't require these selective sample preparation steps, therefore, random access is possible."*

*"Post-run time is also greatly reduced on the Toxyter™ compared to GC-MS. Data-mining is more efficient, and you don't need as much experience."*

Previous comparisons have been made between traditional GC-MS techniques and the comprehensive LC-MSn ion trap spectral library-based forensic screening solution, to differentiate their ability to detect and confirm both parent drugs and metabolites in urine. The results from this study concluded that the Toxyter™ solution reported results of equal or greater value when compared with the GC-MS results. Additionally, some compounds not detected with GC-MS are important drugs of abuse relevance, such as Pregabalin and Ritalinic acid.

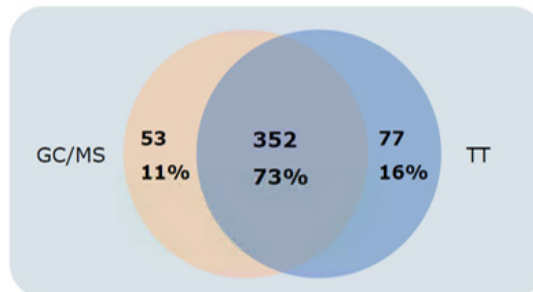


Figure 1: Results from the analysis of 150 urine samples, identified by GC-MS and/or Toxyter™ (TT)

The time it takes the Lab-Dessau to process one urine sample with GC-MS, through enzymatic hydrolysis, extraction, derivatization and chromatographic run with cooling totals 3 hours 25 minutes. In contrast to this, the time it takes to process one urine sample using the Toxyter™ is 1 hour: 30 minutes for extraction and 30 minutes for the chromatographic run. Oral fluid samples require the extraction step, but for urine samples, using the Toxyter™ a simple dilution replaces the extraction process. The overall effect of this streamlined sample preparation is a reduction in losses and minimal selectivity, making way for a more time-efficient process and a better turnaround time for customers. The transition to this instrument enables the laboratory to conduct a higher volume of analyses and therefore service a larger number of customers.

*"In my department, we have been working with Bruker for three years, and the Lab-Dessau as a whole has been working with them for six years. This partnership has enabled us to provide a service to our customers that we never imagined we would be able to before: the addition of general unknown analysis on oral fluid, as well as the faster speed at which we can service our customers has made a huge difference"* comments Dr. Böttcher.

Another benefit of the Toxyter™'s sample preparation method is that, where GC-MS samples are run in batches, with the Toxyter™, when a sample arrives it can be analyzed almost straight away, improving the laboratory's response time and enabling sample analysis at any time of day. GC-MS samples can only be run once or twice per day due to the time consuming hydrolyzing step during sample preparation, which takes 1-2 hours.

This is important in cases of intoxication, explains Dr. Böttcher: *“general unknown analysis often comes in with an intoxication case, where you need an instrument with a quick response time. The Toxtyper™ is ideal for such situations, as intoxication samples can be run overnight, undertaken by people who may not even come from a toxicology field –”*

*“the instrument can be used by anyone. It’s dependable and works all the time, and is constantly on standby.”*

The educational benefit of the Toxtyper™ is also valuable to the laboratory: employees with a variety of backgrounds are capable of using the instrument and therefore the workload can be shared across the laboratory.

## Challenges and Solutions

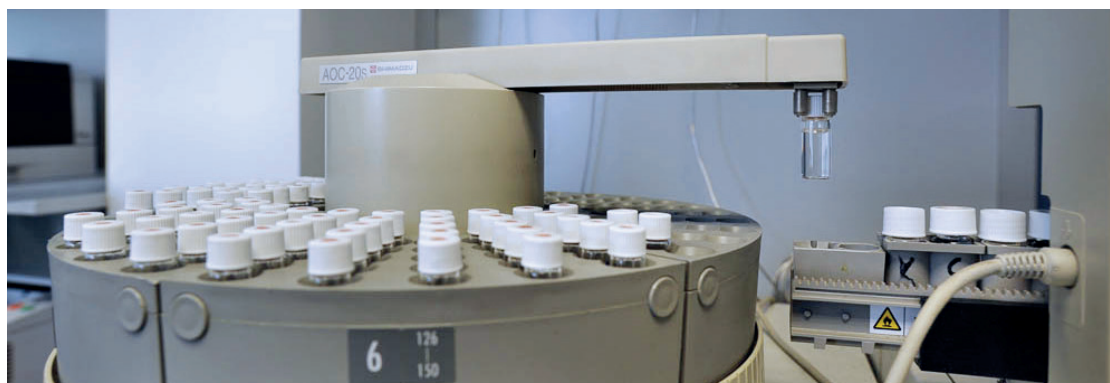
In addition to ultra high performance liquid chromatography, the Toxtyper™ draws upon a comprehensive drug library for toxicological analysis. Dr. Böttcher describes how the availability of such a library facilitates their work:

*“When we heard that a library is available, which is at least the same size as the GC-MS library, but with the addition of glucuronides, we were immediately interested. If the library contains all the important glucuronides, hydrolyzing isn’t necessary. To establish such a library on your own is very complicated, because you can’t buy*

*these glucuronide molecules. Hydrolyzing cleaves the glucuronides, which is time-consuming and selective because some substances are not cleaved 100 percent, and you can’t buy these substances to verify your methods. This is not widespread knowledge, and is an important issue in urine toxicology. The combination of the library containing the glucuronides and the Toxtyper™ instrument is a big success, especially for urine analysis.”*

Dr. Böttcher’s laboratory uses two drug libraries for their toxicology work; one developed by Bruker and one by an external scientific institute (MWW Library). The laboratory uses Bruker’s library, which contains retention time information for nearly 1000 parent substances, for scheduled purposes: there is a narrow detection time window where the substance must be found if it is present. This leads to increased sensitivity as the software is directed to the specific substance. The MWW library contains 1500 substances as well as 3000 metabolites (including glucuronides) and unlike the Bruker library, it is open and is not indexed on retention time. This means that sensitivity is lower, but the library is extremely comprehensive and contains all the necessary substances. Because of this, both libraries are always run on every sample.

*“The two library searches use two chromatographic methods, which is important. All substances which belong together are grouped together in a report, no matter what their position in the chromatogram is – in the re-print they are put in the same group. But if you have a substance which should normally make several metabolites, it’s easy to find as they’re all grouped together. This helps you check your findings for positivity, and you can be quicker in looking for problematic substances”* explains Dr. Böttcher.



A comparative prize-winning study between the toxicological analysis of urine samples using Bruker's Toxtyper™ and GC-MS was conducted by the laboratory: the Toxtyper™ report found 25 substances across both libraries, 9 of which were not found using GC-MS, and the GC-MS report found 14 substances, two of which were not found with the Toxtyper™. After concluding that the Toxtyper™ was superior over GC-MS for urine analysis, Dr. Böttcher tried the same process with oral fluid, with great success. This analysis could then be offered to customers, something not previously achieved before. The subsequent success of using the Toxtyper™ for this level of broad analysis on oral fluid has proclaimed Dr. Böttcher's laboratory as an innovator in the field. Dr. Böttcher explains the discovery:

*"It became clear that the hydrolyzing process for urine analysis is really limiting in GC-MS. If you can avoid it, it's a big step forward. Oral fluid is such a clean matrix; the Toxtyper™ can achieve extreme sensitivity, which was unexpected at the beginning."*

The matrix can have a strong influence on the ionization process of LC-MS. With a clean matrix, the method becomes more sensitive which is advantageous to the laboratory. Previously, oral fluid analysis was impossible using GC-MS because the process was too cumbersome. The laboratory began conducting oral fluid analyses approximately 7 years ago, but it was always targeted. Undirected general unknown analysis only became a possibility once the Toxtyper™ was acquired.

## Future

Due to the rapidly changing industry in which the laboratory conducts their work, new methods must constantly be developed to keep pace with the drugs market. To facilitate this, instrumentation and software must also remain up-to-date. Dr. Böttcher explains some of the areas which could be developed in the near future:

*"I would like to see the external library extended, which should happen this year. There are a lot of new psychoactive substances and synthetic cannabinoids on the market which are not all included. A more frequent update would be useful. We can add substances ourselves, which is an advantage of the urine library: you can buy the parent substances, but you can't buy the metabolites. This is a big argument in favor of this library and of the Toxtyper™ instrument – they have these urine metabolites. For oral fluid and blood, we can add ourselves, because we have the parent substances – many other labs don't even possess the parent drugs. Bruker can extend their library for the modern drugs more often as you only need the parent drugs with oral fluid and blood. With urine samples you need scientific expertise, and the true samples."*

The surge in drug screening demand at the MVZ Laboratory Dessau can be attributed to Bruker's highly specialized instrumentation, directly optimized for the level of sensitivity and broad analysis required for their work.

For more information about the Toxtyper™, please visit <https://www.bruker.com/products/mass-spectrometry-and-separations/lc-ms/ion-trap/toxtyper/overview.html>.

For more information about the MVZ Laboratory Dessau, please visit [www.laborpraxis-dessau.de](http://www.laborpraxis-dessau.de) and for the Limbach Group, please visit <https://www.limbachgruppe.com/fachbereiche/drogenanalytik-und-toxikologie/>

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