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Thinking Small

Pascal Cardinael and Valérie Agasse from the University of Rouen, in Mont-Saint-Aignan, France, reveal the rationale behind miniaturization and the latest developments in miniaturized gas chromatography (GC).

—Interview by Kate Jones

Q. What benefits does miniaturization offer analytical scientists?
Pascal Cardinael: Miniaturization offers new possibilities for analytical chemists and can drastically reduce analysis time, gas consumption, and analysis costs (1). The required quantity of sample is also drastically reduced, which is crucial for high added-value samples or for samples available in very low amounts. Moreover, analyses can be performed directly on site, without wasting time or risk of contamination of the sample. The miniaturization of autonomous systems will also make it easier to implement online process measurement systems.

Q. Could you provide a general overview of miniaturization in gas chromatography (GC) and how it has evolved?
Valérie Agasse: For miniaturized GC, the most important points to improve system portability are to reduce the size and weight of the equipment without loss of chromatographic performance. In most cases, preconcentration is necessary to improve sensitivity because of the lower injection volume. A micro-preconcentrator (2), injector (3), column (4), and a detector based on silicon technology were developed (1,5). This technology was directly transferred from the microelectronic industry. The reduction in battery size and the extension of battery life was significant. This is why it has been essential to reduce the electrical power consumption of the equipment. As the carrier gas container should be included in the system, the decrease of column size allowed the gas flow to be reduced and thus saved.

Q. What have been the main challenges involved with miniaturizing equipment for GC?
VA: The main challenges were to reduce the size of each part of the chromatograph from the injector to the detector and, of course, from the column to the core of the separation system. The choice of the stationary phases remains limited for microcolumns in comparison with conventional capillary columns (1). Our laboratory was involved in the elaboration (6) and coating of stationary phases to extend their selectivity and the possible applications (7). We have recently developed classic stationary phases based on ionic liquid (8), but also sol-gel types (6) that we adapt to miniaturized systems. Moreover, it is necessary to maintain the performance of the chromatographic system with the size constraints in terms of extracolumn volumes. Another challenge to maintain the versatility of GC was the development of equipment with the possibility of heating the injector and of programming the column temperature—as is possible with benchtop GC devices.

Q. Have there been any important developments in miniaturization in GC recently?

PC: The important recent developments concern silicon-based modules, in particular for detection, with the development of nanoelectromechanical systems (NEMS) technology detectors and the coupling with a miniaturized mass spectrometer. Through a partnership with a leading company we are aiming to develop chemical surface modification to tune the detection selectivity of resonant NEMS (9). A very promising new design of silicon-based microcolumn, including pillar array columns for GC, has recently been reported (10).

Q. Could you talk a little about the work you are doing on the miniaturization of columns for the development of a GC system for space missions?

VA: For three years we have been fortunate to work with our colleagues from LATMOS (11) on the elaboration of a miniaturized GC. We are particularly involved in the coating of stationary phases in silicon-based microcolumns. The columns are not much larger than a two euro coin. We hope to obtain very light and robust columns with very different phases to analyze all types of organic compounds including chiral molecules. The first results are very promising.

Q. Where do you see your future research taking you?

VA: Based on our experience in phase
coating, we plan to work on surface treatments to improve the chemical stability and performance of the columns. Improvement of the column design will be another way to increase column efficiency. We will also work on the preconcentrator of the sample, particularly on the trap, to enhance sensitivity.

Q. Are there any misconceptions surrounding the performance of miniaturized GC systems? What advice can you offer to other scientists thinking of using miniaturized systems in their research?

PC: The most common misconceptions about miniaturized systems concern the fragility of the systems, particularly connectors and valves, but modern systems are robust and efficient. Unfortunately, the system sensitivity is often underestimated, but the coupling with the mass spectrometer (12) and NEMS detection (13) has exhibited satisfying sensitivity for major applications. The advice we would give to our colleagues is to clearly define their needs and test one microsystem.

References
Cocaine and Illicit Drug Levels Analyzed in Central London

A group of researchers has investigated the impact of combined sewer overflow (CSO) on pharmaceutical and illicit drug use in central London using liquid chromatography–high-resolution mass spectrometry (LC–HRMS) (1).

The occurrence of pharmaceuticals, personal care products, and illicit drugs in receiving waters has been the focus of many studies over recent years, mainly to see if there is an effect on ecosystem health and directly or indirectly on humans. The predominant identified source is from treated wastewater effluent, which is sometimes ineffective for removing these compounds. Alternative sources do exist and one potential is raw sewage spills, such as those that occur when sewers fill up during times of heavy rainfall and overflow into rivers rather than backflushing up into streets and homes. Leon Barron, lead researcher on this work, said, “This project aimed to identify which drugs might be elevated in London’s Thames River following such sewer overflows. London’s sewage network dates from Victorian times and it simply cannot cope with a population of more than 8.6 million. The Thames Tunnel project is currently underway to tackle sewage overflows by directing them via a ‘super sewer’ to a relief works in East London. This project served as a ‘before’ snapshot of drug concentrations in the Thames River prior to a major sewer infrastructure upgrade to assess impacts on river health.”

There was no major change in drug concentrations during overflow periods for a selection of commonly used pharmaceuticals. However, stimulant drugs like cocaine and caffeine both rose during overflows for about 24 h after the event and subsided then again between 24–48 h afterwards. Leon commented: “We have performed analysis of London’s wastewater for many years and cocaine concentrations have been steadily rising due to increased community consumption. The concentrations in raw sewage regularly exceed 1000 ng/L. Concentrations of cocaine are generally much lower in receiving water (approximately 1–5 ng/L) because it is normally well removed during wastewater treatment, but concentrations still increased by 10-fold after overflows. This was also matched by concentrations of its primary metabolite benzoylecgonine up to 72 ng/L.” The group has also performed a study in Suffolk county, which is a rural site in the east of England (2). “We have been extending our analysis to biota and in this study we were also able to detect cocaine in all shrimp samples taken from 15 sites across this area. In addition to this, we were able to detect ~50 other drug compounds and pesticides, many of which are illegal in the UK. The sources of these compounds remain unclear and perhaps it is linked to sewer overflows across the UK. We are now extending this study to analyze biota samples from across the UK to assess the extent of the problem. We would expect to see cocaine contamination in urban sites like London, but such a remote area was a surprise.”—K.J.

References
**Peaks of the Month**

- **The LCGC Blog: Buffers and Eluent Additives for HPLC and HPLC–MS Method Development**—Modern HPLC method development is dominated by a small number of pH adjusting reagents and buffers that are prevalent even when the method uses UV detection. This is driven primarily by the requirements of mass spectrometry. [Read Here>>]

- **Understanding How Dwell Volume Can Affect Selectivity in Reversed-Phase Gradient Chromatography**—The effect of dwell volume on chromatographic selectivity can be successfully modelled using retention prediction software. Hence, the robustness of reversed-phase LC gradient methodologies, with respect to dwell volume, can be conveniently assessed. [Read Here>>]

- **Tips & Tricks GPC/SEC: How GPC/SEC Can Help to Reduce PET Plastic Waste**—One of the major problems with plastics is recycling. Only a few materials can be recycled and the acceptance of recyclates is sometimes low. GPC/SEC can be applied to investigate the quality of materials containing recycled portions. [Read Here>>]

- **A Design for Life Sciences**—*The Column* spoke to Robert Shaw, Steph Turnbull, and Sophie Bailes from AstraZeneca about their work in quality by design (QbD) in the pharmaceutical industry. [Read Here>>]

- **A Clinical Approach**—Isabelle Kohler from Leiden University, in Leiden, The Netherlands, spoke to *LCGC Europe* about the latest trends in clinical metabolomics using chromatography and how the field is likely to evolve in the future. [Read Here>>]

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**News In Brief**

Shimadzu (Duisburg, Germany) is offering the lab4you student programme for young scientists for the fifth year in a row. Young scientists can apply for laboratory bench space for their own research in Shimadzu’s Laboratory World at their headquarters in Duisburg. “Because of the extensive research environment, providing a unique possibility to work with devices that are best suited to and tailored for the own research, I highly recommend other students to apply for the lab4you student programme”, commented Dr. Carola Schultz, the first lab4you student in 2015. Students can apply in English by submitting a short abstract of their research via [www.shimadzu.eu/lab4you](http://www.shimadzu.eu/lab4you) until 31 October 2019.

Thermo Fisher Scientific (San Jose, California, USA) has announced that it has completed the acquisition of HighChem, Ltd., a developer of mass spectrometry software based in Bratislava, Slovakia. HighChem software solutions are used to analyze complex data and identify small molecules in pharmaceutical and metabolomics laboratories. “The addition of these software solutions to our existing mass spectrometry software portfolio will enable us to deliver greater value for our mass spectrometry customers,” said Mitch Kennedy, president, chromatography and mass spectrometry, Thermo Fisher Scientific. [www.thermofisher.com](http://www.thermofisher.com)
Meeting Review: Latest Advances in the Analysis of Complex Environmental Matrices, 2019

Lee Williams¹, Roger Reeve², and Graham Mills³, ¹School of Pharmacy and Pharmaceutical Sciences, Faculty of Health Sciences and Wellbeing, University of Sunderland, UK, ²Environmental Chemistry Group, Royal Society of Chemistry, ³School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, UK

A biennial meeting jointly organized by the Environmental Chemistry Group, Separation Sciences Group, and the Water Science Forum, and discussing the latest advances in the analysis of complex environmental matrices, is now in its eighth year. The most recent iteration of the event occurred on Friday 22 February 2019 in the Science Suite, Royal Society of Chemistry, Burlington House, in London, UK. This meeting review offers an overview of what is happening in the industry.

Over the last eight years, the Environmental Chemistry Group (ECG), with the Separation Science Group (SSG) of the Royal Society of Chemistry (RSC), has sought to present the latest applications of new and developing analytical techniques to complex environmental matrices. The application of analytical chemistry is common within a large number of disciplines and subject fields. Each area of the application has its own particular challenges concerning sample complexity, treatment, and analysis.

Over the last eight years, the Environmental Chemistry Group (ECG), with the Separation Science Group (SSG) of the Royal Society of Chemistry (RSC), has sought to present the latest applications of new and developing analytical techniques to complex environmental matrices. The application of analytical chemistry is common within a large number of disciplines and subject fields. Each area of the application has its own particular challenges concerning sample complexity, treatment, and analysis.
samples within the area of environmental chemistry.

There are a number of unique challenges within this field and the sheer complexity of the sample, coupled with low analyte concentration, often requires the implementation of novel analytical strategies. If we couple matrix complexity with an important variable within environmental research, spatial sampling, we have a further difficult requirement. This is the recording of not only the type of sample, but also its three-dimensional location within the environment. If we consider that each experiment may be performed over a long period of time using multiple time points, locations, and depths, we can begin to see that large numbers of often uniquely complex samples and data can be generated.

The latest meeting, the fourth of the biennial event, took place on Friday 22 February 2019 at the RSC, Burlington House, in London, UK. The meeting was well attended by over 60 delegates. The joint organizers of the meeting, the Environmental Chemistry Group (Roger Reeve), the Separation Science Group of the RSC-Analytical Division (Lee Williams), and the Water Science Forum (Graham Mills), developed a programme to show the advances within each stage of the major workflow of the discipline; sample collection, sample preparation and clean-up, final analysis, and the ever increasingly important stage of chemometric data analysis. Machine learning, data treatment, and statistical analysis of complex matrices has been seen in a number of fields, such as metabolomics and diagnostic healthcare, for a number of years and the application and benefits to the environmental field is becoming more recognized and widespread.

The first of the presentations on environmental sampling was given by Anthony Buchanan (SepSolve Analytical, UK) with a lecture on the “Enhanced Confidence in River Water Quality Monitoring Using Passive Sampling and GC×GC-TOF-MS (Two-Dimensional Gas Chromatography, Time-of-Flight Mass Spectroscopy) with Tandem Ionization”. Perhaps obviously, the role of routine environmental monitoring is to ensure the quality of the environment and provide safety to those within it. Evaluating a particular location using grab or instantaneous sampling may miss important pollution events and, therefore, the use of long-term passive sampling may be more suited. Current challenges for this type of analysis include new “priority” substances and emerging pollutants.

A silicone rubber passive sampler was used to collect and concentrate hydrophobic substances in this investigation with four weeks sampling time, on a river system at eight different locations.

...
Figure 1: Comparison of individual spot sample and time–weighted average concentrations. Reproduced with permission of G. Fones, University of Portsmouth, UK.

Analysis was performed using two-dimensional gas chromatography, a tool that is becoming more common in complex sample analysis. Flame retardants, fragrance bases, and pharmaceuticals were detected. A novel approach to sample identification was implemented using fast switching between high eV and softer, low eV ionization voltage in the ubiquitous electron ionization (impact) source. This produced two MS datasets from a single run with no added analysis time, but extended the quality of the mass spectra and ability to retain more of the molecular ion to aid in compound identification.

The limitations of grab sampling were a theme further developed by Gary Fones (University of Portsmouth, UK) with his talk: “Can Passive Sampling Devices Provide More Useful Data than Discrete Samples?”

Passive samplers offer long-term monitoring, identifying pollution trends, time frames, and patterns, and can locate sources of pollution with more robust time integrated data than instantaneous sampling. Grab sampling provides only a “snapshot” of the pollution situation (Figure 1) and may not be representative of occasions where concentrations of individual pollutants...
fluctuate or where the overall composition may not be homogeneous.

A passive sampling device, designed to monitor a wide variety of pollutants in a range of aqueous environments, was chosen for the analysis of polar pesticides in the River Rother catchment system (West Sussex, UK). A total of 14 sites and a two-week continuous sampling time was chosen for the study. The analysis was performed using liquid chromatography quadrupole time-of-flight mass spectrometry (LC–QTOF-MS). The advantages of QTOF, namely a high specificity, sensitivity, accurate mass, and large dynamic range, provided the ability to consistently identify and determine the relative levels of 51 compounds within the river system. The data demonstrated that the concentrations of pollutants was in flux within the sampling period, something that would not have been evident within a single time-point sample.

An additional approach to long-term monitoring was presented by Alistair Boxall (University of York, UK) in “Temporal and Spatial Variations of Pharmaceutical Contamination in an Urban River System”. This research took point samples at 11 sites entering the River Ouse system (Yorkshire, UK) monitoring 41 pharmaceuticals using repeated grab, rather than passive, long-term sampling. This built up a detailed model through which it was possible to predict time-based variations of individual pollutant concentrations at each section of the river system. It was noted throughout this study that pollutants decreased significantly, sometimes to effectively zero, depending on the substrate sampled, in particular, those substrates that were washed away during storms. The model could be successively upgraded as more local details of the river system are introduced. Monitoring of pharmaceuticals in this way has been extended to a global network and subsequent correlation of the results suggests a greater problem of high concentrations in lower income countries.

The use of multiple point samples rather than long-term passive sampling was described through the lecture by Katie Read (National Centre for Atmospheric Science, NCAS, University of York, UK), who introduced the challenges and implications of the use of “GC–TOF for Remote Monitoring—Cape Verde Atmospheric Laboratory”. Using remote, automated equipment (Figure 2) posed many challenges when setting up the distant laboratory and much of the talk discussed additional problems of atmospheric analysis in a laboratory located in the midst of the Atlantic. Atmospheric dust, salt crystal formation, sea water, and abrasive particles of volcanic rock each contributed to enhanced corrosion on the instruments. The air masses passing the laboratory were from a variety of origins and specific effects could be observed from those arriving from Africa, Europe, and North America, in addition to pristine Atlantic air. Despite this, both in situ measurements and sampling with subsequent laboratory analysis were used to monitor air samples.

The results of the comparison between existing GC–MS and new GC–TOF-MS analytical instruments demonstrated a reduction in the sensitivity gap between quadrupole and triple quadrupole systems over QTOF mass analyzers. Results from the laboratory suggest that 50% more ozone is destroyed in this region than was predicted by the climate models as a result of the catalytic destruction by natural halogens in sea spray.
In addition to automated sampling, automatic sample preparation was discussed by John Quick (ALS Environmental Ltd.), who presented “Exploring the Advantages of Automated Sample Preparation and GC-TOF-MS for Semivolatile Organic Compound and Pesticide Analysis in Environmental Waters”.

Environmental samples are frequently large volumes, hundreds of millilitres compared to the tens or sub-millilitre quantities found in clinical or pharmaceutical samples. The requirements of analyte extraction and preconcentration before analysis can lead to laborious and time-consuming sample preparation. Using automation in this process provides advantages in terms of increased method accuracy and precision and the ability to use lower sample volumes through more efficient processes and the reduction of consumables.

In the analysis of alkylphenols and ethoxylates, the sample was simultaneously extracted and derivatized. In a second example, automated use of liquid–liquid extraction in a dispersive liquid–liquid microextraction (SPE) technique was used. This method offered time and sample saving over standard liquid–liquid and solid-phase extraction (SPE) techniques.

As is ever the case in progressive measurement science, where data can be collected both rapidly and in increasingly larger quantities, the use of advanced chemometrics to perform data mining experiments, prediction of analyte properties, and characterization of unknown compounds has led to an ever increasing uptake of this approach within environmental research.

This was first demonstrated in the presentation by Leon Barron (King’s College London, UK), whose lecture on “Mixing High Resolution Chemical Analysis and Machine Learning in Ecotoxicology for Aqueous Invertebrates” sought to demonstrate new protocols using new and existing tools for the analysis of unknown chemical entities.

Samples were taken from water, fish, and invertebrates. The samples were analyzed, first in a targeted approach, using LC tandem mass spectroscopy (MS/MS) allowing characteristic fragments to be recorded. Suspect compound screening was undertaken by LC–high-resolution mass spectroscopy (HRMS) to provide a higher level of mass accuracy, which greatly aids the identification of unknown analytes.

The use of machine learning provided a good predictive model of retention time on LC stationary phases and was further developed to bio-concentration factors. This was the first of two lectures highlighting the use of computational techniques in chromatographic data analysis to aid compound identification, prediction of chemical properties, and possible environmental effects. The keynote speaker, Emma Schymanski (Luxembourg Centre for Systems Biomedicine, Luxembourg), illustrated further with her presentation on “Environmental Informatics to Identify Unknown Chemicals and Their Effects”, which discussed the number of European, US, and worldwide community initiatives to help connect chemistry and toxicity with environmental observations.

Within the work, 364 targets were identified in Swiss wastewater. Targeted, suspect, and nontarget screening is required to attempt to identify the number of unknown compounds within the environmental system. Compound characteristics can be built using a number of known compounds (targeted) and confirmed in a number of available databases. Suspect screening involves selection of candidates based on known and calculated physical properties. The implementation of a workflow involving several mass spectral libraries was used in an attempt to identify compounds, as many libraries whilst overlapping, had unique entries.

It was noted by many attendees that one of the most impressive aspects of the work was the level of cooperation and data exchange between research groups. The NORMAN
network within the EU exchanges information on emerging environmental substances, their validation, and harmonization of analytical techniques. In this investigation the NORMAN suspect list exchange and its chromatography data bank (digital sample freezing platform) were used and have been made freely accessible to anyone who requires it. In this way the more the algorithms and databases are enhanced and added to, the greater the probability of compound identification.

The final theme of the event, moving from identification of unknown substances, was the characterization of the specific pollutants in environmental matrices.

The first of these was a presentation by Caroline Gauchotte-Lindsay (University of Glasgow, UK) on “Micro- and Nano-Plastic Pollution of Freshwater and Wastewater Treatment Systems”. Her group has been attempting to investigate not only the range of plastics, but also the different morphologies present.

The demonstration of contamination of marine organisms and water samples by nanoparticles has, in recent years, been elevated from academic research articles and conferences to the forefront of discussion within the general media and is a concern for public health and the marine environment.

Gauchotte-Lindsay showed that nanoparticle contamination can be fibrous as well as the more expected, solid bead-type. These different morphologies may change how the pollutant behaves in the environment.

After pretreatment, sediments were investigated by scanning electron microscopy (SEM) coupled with energy dispersive spectroscopy (EDS). Fibres were found to comprise approximately 88% and 95% of all plastic pieces. Characterization of water samples was undertaken by Fourier-transform infrared attenuated total reflectance spectroscopy. It was further demonstrated that fibres were predominantly plastics (58% polypropylene and 5% polyethylene), the rest being cellulose (11%) or of unknown composition.

The final session of the day was a presentation by Wai-Chi Man (Thermo Fisher Scientific, UK) on the “Power of Ion Chromatography with Mass Spectrometry for Polar Pesticides in Water”. Ion chromatography (IC) has often been thought of as a specific technique used only for the analysis of inorganic ions. However, she showed that the method was more than this single use strategy and was suitable for the separation of highly polar species as well as ionic species in samples.

Polar pesticides in both food and environmental samples were determined at levels well below US Environmental Protection Agency regulatory limits without chemical derivatization using IC–MS, and the technique itself was shown to have a very low chemical noise, thereby reducing interference.

The presentation closed by posing a question based upon a conversation about a separation that had been developed, but which reaches to the core of analytical science; whether the user wants a slow separation of all possible components, or a more rapid analysis where there was peak overlap of the main analyte of interest with other species.

The answer depends, of course, on the application, but reminded us all of the multiple and sometimes conflicting choices needed in deciding the most appropriate analytical technique.

Acknowledgements

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Lee Williams is senior lecturer in analytical chemistry at the University of Sunderland. His interests are the analysis of compounds in highly complex matrices using hyphenated techniques and the use of chemometrics to provide robust statistical validation.

Roger Reeve has recently retired from the University of Sunderland where he was senior lecturer. His interests, are instrumental analysis of environmental pollutants and the behaviour of pharmaceuticals in the environment.

Graham Mills is professor of environmental analytical chemistry at the University of Portsmouth. His interests are measuring pollutants in water using novel monitoring devices combined with chromatographic and mass spectrometric analytical techniques. He was the inventor of the passive sampler described in this article.

E-mail: lee.williams@sunderland.ac.uk / rgrreeve@gmail.com / graham.mills@port.ac.uk
Website: www.rsc.org/Membership/Networking/InterestGroups/Environmental/
The **LCGC Blog**: HPLC Diagnostic Skills—Noisy Baselines

**Tony Taylor**1,2, 1Crawford Scientific, Strathaven, UK, 2CHROMacademy

In this instalment of the **LCGC Blog**, Tony Taylor discusses noisy baselines in high performance liquid chromatography (HPLC).

Just as medical practitioners are able to discern worrying features from a variety of medical physics devices (electrocardiogram, electroencephalogram, and ultrasound, for example), we need to develop the skill to identify worrying symptoms from our high performance liquid chromatography (HPLC) instrument output. Medical professionals learn an innate ability to identify critical symptoms (signals) from the noise or random variation in the instrument output, and we need to develop these same skills in order to avoid production of data not fit for purpose or instrument failure.

One of the most useful diagnostics in HPLC is the nature of the baseline produced by the detector while the eluent is flowing. While there can be many baseline characteristics such as drift, irregular, or more regulation cycling (pulsations), baseline noise is perhaps the most commonly encountered, and can arise from a variety of different sources. One needs to be aware of what constitutes “normal” baseline as opposed to unusual levels of baseline, depending upon the instrument configuration. Of course, the business imperative is not only to spot problems, but also to quickly and efficiently deal with them, and that is the subject of this blog.

The signal to noise (**S/N**) of the HPLC output is usually measured as the ratio of the detector signal to the inherent background signal variation and is a useful measure of the “normal” noise within the system. The inherent or background noise is typically measured over a predefined...
The smallest detectable signal is usually estimated to be equivalent to three times the height of the average baseline noise. This would give a $S/N$ ratio of 10:1 for the “limit of detection” (LOD) of the detector. If the amount of analyte injected is less than this, then the signal ceases to be distinguishable from noise. For quantitative analysis a $S/N$ ratio of 10:1 is recommended for the “limit of quantitation” (LOQ).

The magnitude of the analyte signal cannot be used in isolation when calculating detector sensitivity, the sensitivity of detection is usually defined in terms of $S/N$ ratio—a measurement of the ratio of the analyte signal to the variation in baseline. $S/N$ measurements are usually performed by the data system.

One needs to begin by establishing, preferably for each method and set of systems, a portion of the baseline, and most data systems will be capable of making this measurement and reporting the result.

When inherent or background noise within the system is unusually high, this can affect system performance and will usually result in an increase in the limit of quantitation and issues with reproducible integration. This is why, as chromatographers, we get so worked up about noise levels that are higher than expected.

Detector Sensitivity

![Figure 1: Signal (S) to noise (N) measurement of 5:1.](image)

![Figure 2: Determination of $S/N$ ratio and the independence of absolute signal intensity on signal-to-noise ratio.](image)

$S/N = 1 / 0.1 = 10 \text{ TO } 1$

$S/N = 0.25 / 0.01 = 25 \text{ TO } 1$
instrument conditions, the S/N when the method (or instrument) is performing well, and perhaps even set a system suitability performance criterion (usually a range or lower acceptable limit) for the determination.

Of course, the seasoned chromatographer will typically know by glancing at the baseline whether the inherent noise is “usual”, and this comes only through experience. One should also take care to assess the noise at a reasonable screen magnification or signal attenuation, as any baseline can be made to appear noisy with the correct level of magnification!

However, once again the data system may be able to help us out by reporting what is known as the peak-to-peak noise, which may be expressed as absorbance units. This measurement is of the variation in the normal baseline portion, rather than a ratio to the height of a signal, and can be very useful at establishing acceptable limits for the background noise. Most HPLC detectors will run a noise test evaluation as part of their initialization routine or can perform a longer test using ASTM criteria with HPLC-grade water flowing through the flow cell. Specifications for acceptable noise levels will be given in the manufacturer’s literature.

Although typically associated with detector phenomenon, there are many
Figure 7: Relationship between baseline noise and sampling frequency (data acquisition rate) in UV detection.

Figure 8: Baseline spikes caused by UV detector lamp arcing.

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Contributors to the noise within an HPLC system, and here we will examine just some of the main culprits. Noise can be both random and periodic depending upon the nature of the underlying cause of the problem, and this difference can, in itself, give us some clues to the nature of the issue.

Detector Noise

Electronic and Stray Light Noise:
Every detector has associated background electronic and stray light noise, which is kept to a minimum through shielding of the optical bench with insulating materials. The in-built tests within the detector firmware should keep this to a minimum, and the instrument will flag up if any of these tests are failed on start-up. This is a good reason to cycle the power on the detector every now and then if your laboratory practice is to leave the detector powered on when not in use.

Detector Wavelength and Acquisition Settings: Lower wavelength settings (<220 nm) will inherently show an increase in noise that is associated with solvents (methanol absorbs up to 201 nm) and buffers that lower the amount of light falling onto the photodiode array. The noise of the detector is inversely proportional to the amount of light falling on the photodiodes, and therefore any other factors that decrease the amount of light falling onto the photodiode will also increase the noise within the output. Typically, this can include an ageing lamp or dirty flow-cell windows.

These problems may be overcome in the following ways:
- Follow your manufacturer’s instruction to clean or replace the flow-cell windows
- Perform a lamp intensity test (using on-board diagnostics) to assess lamp performance and replace the lamp if necessary
- Use acetonitrile instead of methanol as

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**Figure 9:** Comparison of UV absorbance signals (214 nm) obtained with different mixers in use. The same pump was used as in Figure 5, but now with a column (30 mm × 2.1 mm i.d. Agilent SB-C18) in use, and gradient elution. Solvent A is 0.1% trifluoroacetic acid in water, solvent B is 0.1% trifluoroacetic acid in acetonitrile, and the gradient runs from 2 to 40% B in 4 min (1).

**Figure 10:** Baseline noise caused by eluent out-gassing the flow cell of a UV detector.
the organic modifier (methanol cut-off 210 nm)
• Avoid using highly absorbing buffers and additives that include (UV cut-off shown in brackets for a 10 mM solution): TFA (0.1% TFA shows much lower absorbance at 214 nm than 210 nm), citrate (230 nm), acetate (210 nm), formate (210 nm)
• Optimizing the compressibility and stoke volume settings of the pump to minimize the noise based on the compressibility of the solvents used.

Most diode array UV detectors have a slit width setting that describes the width of the slit that focuses light onto the photodiode after passing through the flow cell. As the slit width is increased, the light becomes more diffuse and each wavelength falls over a number of photodiodes (corresponding to the slit width setting). This reduces the noise of the baseline while increasing the signal intensity and so gives greater analytical sensitivity when quantifying analytes. However, the spectral resolution necessary for qualitative analysis (peak track via library matching, for example) is lost, and so it needs a much narrower slit width setting so that the light is less diffuse and each wavelength falls on a smaller number of diodes. When slit width is reduced, the noise level increases, and one needs to set width according to the analytical requirements.

The detector acquisition rate and data bunching may also have a profound effect on signal noise according to the following relationship:

\[ \text{Noise} \approx \frac{1}{\sqrt{n}} \]  

Where \( n \) is the number of data points. Simply put, the more measurements that are taken, the better that we model the random variations associated with instrument response change and the noise becomes better resolved. One needs to carefully balance the \( S/N \) ratio with the actual peak to peak noise generated, which is usually achieved using the instrument response or frequency. This needs to be further balanced with the number of data points acquired across each peak, which should be in the region of 20–25 or higher for UV data.

As alluded to earlier, the deuterium lamp within the UV has a finite lifetime, and can lead to not only an increase of baseline noise, but also to spikes as the lamp arcs against the metal casing onto which the filament is mounted. This gives a baseline appearance similar to that shown in Figure 8, and one needs to consider lamp replacement to judge if the spiking is due to the age of the lamp. Note that other causes of baseline spikes (such as a poorly shielded electrical supply or power board within the detector) are also possible.

Spikes can be distinguished from “real” peaks as they will have no Gaussian shape when zoomed in.

**Other Sources of Noise**

**Improper Mixing:** HPLC UV detectors can be very susceptible to improper mixing of mobile phases, which are formed on-line via either binary or quaternary pumping systems. The absorbance changes as a result of poor mixing are usually associated with a sinusoidal pulse (covered in a future blog); however, at lower pumping volumes or when using additives such as TFA, the disturbances can resemble noise rather than a discernible sinusoidal pulse.

Figure 9 shows the differences made to the baseline appearance of a 0.1% TFA gradient with various mixer volumes.

Even though modern HPLC instruments are designed with high-efficiency mixers, the addition of a post-market static mixer or simple in-line filter can help to drastically reduce the baseline noise under the circumstances described above. One should note that the additional extracolumn volume contributed by
the fitting of in-line mixers may have a detrimental effect on peak width, especially in ultrahigh-pressure liquid chromatography (UHPLC) systems, and one needs to balance any increase in peak width with the reduction in baseline noise when assessing the S/N characteristics of the method.

One should further note that very similar noise characteristics can also be obtained from failing quaternary pump gradient proportioning valves.

**Lack of Degassing:** If the mobile phase is poorly degassed, small bubbles may outgas from the mobile phase as the eluent enters the flow cell of the detector, due to the pressure change that occurs. This “frothing” of the mobile phase can cause significant baseline noise, and while detector flow cells are designed with a back-pressure restriction to reduce the pressure reduction on entering the flow cell, this can be ineffective when the eluent is not properly degassed.

One needs to ensure that the eluent is properly degassed using on-line degassing modules and, in some cases, by degassing using vacuum methods prior to mounting onto the HPLC system.

**Dewetting:** If the HPLC column contains residual packing solvents or has been used with immiscible solvents (for example, in normal phase mode), then improper flushing of the column can lead to increased baseline noise associated with dewetting phenomenon. Equilibrate the column for several hours at the method flow rate to completely flush the column of any immiscible solvents.

**References**
1. https://www.researchgate.net/post/How_can_a_very_high_noise_signal_in_HPLC_Diode_Array_detector_be_explained

**Tony Taylor** is the technical director of Crawford Scientific and CHROMacademy. He comes from a pharmaceutical background and has many years research and development experience in small molecule analysis and bioanalysis using LC, GC, and hyphenated MS techniques. He is actively involved in method development within the analytical services laboratory at Crawford Scientific and continues to research in LC–MS and GC–MS methods for structural characterization. As the technical director of CHROMacademy, he has spent the past 12 years as a trainer and developing on-line education materials in analytical chemistry techniques.

E-mail: tony@crawfordscientific.com
Website: www.chromatographyonline.com
The 30th International Symposium on Pharmaceutical and Biomedical Analysis (PBA 2019)

A preview of the upcoming 30th International Symposium on Pharmaceutical and Biomedical Analysis (PBA 2019), which is due to be held on 15–18 September 2019 at the Convention Centre of The Dan Panorama Hotel in Tel Aviv, Israel.

The organizing committee invite you to come to the 30th International Symposium on Pharmaceutical and Biomedical Analysis (PBA 2019), which will be held 15–18 September 2019 at the Convention Centre of The Dan Panorama hotel in Tel Aviv, Israel.

It follows a series of successful PBA symposia organized all over the world since 1987, when the first International Symposium on Pharmaceutical and Biomedical Analysis (PBA) was launched in Barcelona, Spain. Now, for the first time in its history, the symposium arrives in the Middle East.

The symposium will cover all aspects of pharmaceutical and biomedical analysis, including new analytical technologies and methodologies for (bio)pharmaceuticals, biomarkers, and “omics”. A special session will be focused on the emerging field of medical cannabis. It is in the spirit of this symposium series to attract researchers from all over the world, from a broad range of areas involved in drug analysis, related materials, and endogenous compounds.

Plenary and keynote lectures will be given by internationally recognized invited speakers. A number of materials will be presented as oral communications and poster presentations. Participation of young researchers, both from industry and academia, will be strongly supported by a dedicated young scientist session, best oral presentation, and poster awards, as well as a reduced registration fee and affordable lodging.

PBA 2019 will also offer stimulating and highly informative workshops by recognized experts in their field; these will be run in parallel on Sunday 15 September from 9:00 to 13:00. These workshops include:
• "Solid-phase microextraction (SPME) in medical and translational research" given by Janusz Pawliszyn and Barbara Bojko from Waterloo University, Canada

• "Advanced CE–MS and NMR approaches for metabolomics" given by Rawi Ramautar and Oleg Mayboroda from Leiden University, the Netherlands

• "API solid state characterization in preformulation studies" given by Judith Aronhime, consultant on pharmaceutical polymorphism and solid state analysis, Israel

Participants are also invited to submit manuscripts based on presentations at the PBA 2019 meeting for possible publication in the Journal of Pharmaceutical and Biomedical Analysis (JPBA), with the intention of publishing a special issue dedicated to the meeting. Such special issue publications essentially rule out possible delays for contributors.

One of the major aims of the symposium is to provide a forum for high-level scientific exchange between analytically oriented scientists from the whole world in a friendly atmosphere.

Tel Aviv, with its special cosmopolitan atmosphere, can offer excellent opportunities for scientific, cultural, and social experiences in a unique Mediterranean seaside setting. The symposium venue is located within walking distance from Old Jaffa. This ancient city with more than 3000 years’ history is in the oldest part of Tel Aviv, and is famous for its association with the biblical stories of Jonah, Solomon, and Saint Peter, as well as the mythological story of Andromeda and Perseus.

An attractive programme of social events will also be arranged during the symposium, including a full-day guided tour to Jerusalem on 19 September.

As a country geographically bridging Europe, Asia, and Africa and located on the crossroads of culture and religion, Israel enjoys the established status as one of the most popular tourist destinations.

The organizers look forward to seeing you in September 2019 and wish you a fruitful and enjoyable stay in Israel.

More details on the topics, invited speakers, registration, abstract submission, conference fees, and important dates can be found on the conference website: www.pba2019.org.
A Whole Lot of Data Going On

Book Review: Data Integrity and Data Governance by R.D. McDowall

Siri H. Segalstad, Segalstad Consulting AS, Jessheim, Norway

R.D. McDowall has written an excellent book on data integrity and data governance. Those who need to understand what this is should read the book and follow his advice. He has included both what the regulations and regulators say and what we need to do to be in compliance. This is a scalable approach with enhancements for larger items and shortcuts for smaller items, with numerous examples throughout the book.

Twenty years ago the big buzzword in the pharmaceutical industry was 21 CFR Part 11, which was the US Food and Drug Administration’s (FDA) new standard for electronic records and electronic signatures. Discussions raged about how to interpret the standard and how strict it should be. 21 CFR Part 11 actually only had 2.5 pages of requirements, and that was probably one of the most expensive 2.5 pages written, at least for the pharma industry. Maybe until now.
The newer buzzwords have been “data integrity” and “data governance”, which have been floating around for a while. Every agency (FDA, WHO, MHRA, PIC/S, GAMP, and several others) worth its salt has published some requirements of their own about the subject. There are also the good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP) in their many variations around the world that have to be followed for production and analytical laboratory work, nonclinical testing, and clinical testing. Most of them include something about data integrity, maybe not always using that terminology, but they have text that can be interpreted as meaning “data integrity”. So how on earth do we navigate through this enormous mass of requirements?

The answer lies in R.D. McDowall’s newest book Data Integrity and Data Governance—Practical Implementation in Regulated Laboratories (Royal Society of Chemistry 2019). This is a massive tome of 600 pages, and may seem like a tough one to digest with content that may not be all that interesting. Still, the management of regulated industry needs to read all 600 pages in the book in order to set the standard for how every single person in their organization needs to work—their own about the subject. There are also the good manufacturing practice (GMP), good laboratory practice (GLP), and good clinical practice (GCP) in their many variations around the world that have to be followed for production and analytical laboratory work, nonclinical testing, and clinical testing. Most of them include something about data integrity, maybe not always using that terminology, but they have text that can be interpreted as meaning “data integrity”.

The book is not just another boring text book. It has a lot of fun comments scattered inside the text. One example is “Human inventiveness knows no bounds when it comes to data falsification”, and another “the poor reader must hack through a jungle of words to figure out what is needed—this being the analytical equivalent of an Indiana Jones archaeological expedition”, which is the explanation to the data integrity guidance documents from the authorities! McDowall has done the excavation of this giant mass of paper for us.

The book explains in detail all the aspects of the topics of data integrity, starting each chapter with the regulatory basis for each of them. McDowall has made it a lot easier for everyone by publishing this book. The amount of investigations that he has carried out in order to establish a system in the overwhelming craziness of regulatory documents is astonishing. Every manager and every other person that has to make sense out of all this should be thankful that he has cleared an understandable path through this jungle of words and requirements.

While 21 CFR Part 11 was a job to be done (making sure that all the IT systems were OK), data integrity is different. It is a mindset and has to be worked on continuously by everyone in the organization without exception. Or, as the author writes, it is a programme, not a job to be done.

From my own experience, if management is not involved, things will not be done. If management does not require work to be done in a specific way, there will always be people who could not care less about following procedures, especially if it is easier or quicker not to do so. All the things that need to be in place for good data integrity will never be in place unless management itself takes an active part and interest in the work and sets requirements for everyone in the organization to follow. This is actually no different from any quality work, but the data integrity work is even more ubiquitous in the organization.

Poor management; they have to deal with a lot. Quality assurance and quality control require management involvement, reviews, and assessments. Throughput of the work in production or the laboratory requires management involvement, risk analyses, assessments, and maybe changes to the processes. Then there are all the business aspects. Is there no end to what management needs to be involved in? Maybe there is, but data integrity is definitely not one of them.

Before the book even starts, there is a comprehensive glossary covering words, abbreviations, and data integrity terms. Chapter 1 is about how to use this book—useful reading before diving into the rest of the book.

Every chapter starts with an overview and includes citations of relevant parts of the various regulations. It is followed by a small summary from the author, before the detailed explanations about the topic and how to comply. At the end of the chapter there is a comprehensive reference list, and throughout the text there are references to other chapters, other texts, and other books. If you want to read more, it is easy with these references.

The first few chapters start off with the background, and include citations from several warning letters from the FDA to organizations that did not have their data integrity in place. The warning letters from the FDA should be read because these show the current views that the FDA hold. Data integrity problems vary from a basic lack of data integrity and documentation to fraud. Several of these warning letters form the background for the regulatory agencies to respond with more detailed requirements.

McDowall has created a very useful data integrity model in chapter 5 that puts the various parts of the topic in their right place. The foundation requires the right culture and ethos for data integrity. The foundation needs to have management leadership,
policies, procedures, and staff training. Hence the management involvement. For process development and production, the levels above include the right equipment for the right job (including validation and qualification); the right manufacturing process for the right job (including validation and on-going control); and batch manufacturing for the right product (with data supporting the right quality of the product and records meeting the marketing authorization). For analytical development and quality control, the corresponding levels are right instrument and systems for the right job (including qualification and validation); the right analytical procedure for the right job (including validated and verified under the right conditions); and the right analysis for the right reportable result (complete, accurate, and consistent). If the foundation is not in place, the levels above will not work. And if level 2 is not in place, level 3 will be compromised. McDowall has produced a system out of the various requirements with his model.

Other chapters go into detail with each subtopic. Topics include roles and responsibilities, policies, procedures, and training, and how to keep an open culture for data integrity. An open culture means that it should be possible to be a whistleblower or admit to errors without fear of retaliation. In some cultures this is a very different mindset and may be almost impossible to follow. For others it may be difficult if people’s performance is measured by throughput and correctly doing their work. Within a good “quality culture”, finding errors is positive because that means improvement can be made so that the same error is not made again.

McDowall then moves on to the analytical data life cycle, assessment, and remediation of laboratory processes and systems. There is a lot of information about paper records, electronic records, and hybrid systems, which include both paper and electronic records. He strongly advocates getting rid of paper altogether, which is not news to anyone who has worked with 21 CFR Part 11 over the past 20 years. He also covers data integrity of analytical instruments and their qualification as well as computerized system validation. How to validate analytical procedures is covered in detail, and this validation needs to be in place before anyone starts performing analytical procedures. Some regulations call for second person review, and when and how to do this is also discussed. A difficult aspect in any quality work is the quality metrics, and the same goes for metrics for data integrity. He explains how to do this, and also how to raise data integrity concerns.

Data integrity audits are quite equivalent to any other quality audit, but include different checkpoints. How to conduct a data integrity investigation is also covered as well as corrective actions and preventive actions (CAPA). Outsourcing is common in the pharmaceutical industry, and checking that the company does the work includes, of course, a check on their data integrity. There is also a list of items to include in the contract between the company and the work the outsourced company does. The final chapter is a data integrity treatise and lists all the items that need to be checked during an audit. It is not a checklist, and the author advises auditors not to use a one during an audit because that may limit them in their investigation.

Each of the chapters have many examples to show the practical implications of the requirements. Known analytical methods are discussed in detail. One example is observation methods (looking at the sample to assess colour, looks, and smell): should this be documented on paper or electronically? Second person review of the method includes checking that what has been documented on paper has been entered correctly into the laboratory information management system (LIMS). Or should there be some other verification of the result? Another is chromatography methods: what are the raw data? The chromatography data system (CDS) as a stand-alone system needs to be handled and controlled one way, while if it is on the network and also connected to a LIMS it should be handled differently. What about the simple process of weighing a sample? How do we document this in order to have data integrity?

The audit trail is important in any computerized system because this shows when who has done what, and also why anything has been changed. The automatic audit trail includes both first entries and changes. Requirements are that the audit trail is connected to the data and that this is possible to review. Most of the instrument systems as well as LIMS have had this functionality built in for decades, but we need to prove that it cannot be turned off and has not been turned off at any time to prevent fraud.

Computerized systems also need to have named user accounts and no “multiple-user accounts” like an analyst, and each user should have access to what he or she needs and no more. What do you do if you have a user who is not only a user, but also an application manager with many privileges? How can changing time on the computer, turning off the audit trail, or deleting records be prevented? We need to prove that
nobody has access to the back door of the system to change times, audit trails, or other data. The book discusses this in detail.

The many examples in the book are familiar events that happen in the laboratory, like familiar analytical methods are familiar events that happen in the laboratory, like familiar analytical methods. The book discusses this in detail. nobody has access to the back door of the laboratory, like familiar analytical methods are familiar events that happen in the laboratory, like familiar analytical methods. The book discusses this in detail.

For every organization a risk-based approach should be created, and the key to this is to first understand your own processes and go from there. The lists give a good overview after reading the text, but the reader is encouraged to use their own head and make a correct assessment based on their organization, their processes, and the tools they have available. The lists then come in handy because it is possible to pick and choose from them to do a good (or perfect?) job in your own organization. Personally I think that the lists get me thinking in the right direction, and points can be added or deleted once I understand what is needed for my organization. In this respect the content of the whole book is scalable, but you first need to understand what data integrity really is all about. That is no different from all "quality thinking".

When one has read the whole book (or at least most of it), a chapter can easily be re-read and sense made of whatever specific theme the chapter covers, as it contains all the regulatory background, the explanations, and the how-to. Such free-standing chapters mean that there are repetitions in the text, but it also means that each chapter can be read by itself. My opinion is that this is a good approach, even if that results in more pages than strictly necessary.

What I really like about the book are the figures, flowcharts, and tables, which summarize the text very well. But the publisher has made it hard for the readers, as some of the figures are set with fonts that are difficult to read or incredibly small. Some figures have uneven fonts, which results in divided words, like in 2.2 where it says, "No separation of sys tems" and "responsible". They have used half a page for figure 16.1 where the capital letters are 1 mm, instead of a full page that would be far more readable. Some of the tables are very long and could benefit from a little space or a horizontal line between the various parts. Column one has a key word and column two has several points belonging to that key word. If you read column two, you frequently continue on a new key word as there is no space there to show that this is the end.

A few sentences could definitely have been made shorter by adding a comma or dividing the sentence. The problem with the English language is that many nouns and verbs are the same, and you need to understand from the context if it is a verb or a noun. When sentences are up to five lines long without anything to break them up, they may need to be read a couple of times before you understand them. There are a few examples of this, but it is not a general problem.

The book is mainly focused upon the laboratory and the pharmaceutical industry. Every industry and any type of work (for example, production, testing laboratories, healthcare, forensics) would definitely benefit from reading this book if they need data integrity. And data integrity is something everyone should worry about. It only takes a little translation to change the word "lab" to whatever your work is about. The details in the text can also easily be translated to your line of work to get you thinking in the right direction. The pharmaceutical standards cited are in principle not very different from other quality standards. It would definitely help to see what the pharmaceutical standards say, even if you work with International Organization for Standardization (ISO), ASTM, healthcare standards, or any other standards. Data integrity is everything. If you don’t have data integrity you really cannot trust your data.

Siri Segalstad has worked with LIMS and all aspects of IT systems validation for over 30 years, first as an employee with a pharmaceutical company, and then with her own consulting company since 1995. She took part in a EU Leonardo da Vinci project to create a complete master’s degree in IT validation. As a result of this, she wrote the book International IT Regulations and Compliance, which she used when teaching at the Hogeschool Gent in Belgium. In addition, she has written a large number of publications and given classes and presentations from Taiwan in the east to California in the west. She is based in Norway.
### Training Courses

#### GC
**The Theory of GC**  
*Website:* www.chromacademy.com/gc-training.html

**Data Analysis and Sampling Techniques for GC and GC–MS**  
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The Open University, Milton Keynes, UK  
*Website:* www.anthias.co.uk/training-courses/data-analysis-and-sampling

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#### HPLC/LC–MS
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*Website:* https://www.crawfordscientific.com/training-consultancy/other-chromatography-courses/introduction-to-biopharmaceutical-hplc-and-lc-ms-analysis

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The Open University, Milton Keynes, UK  
*Website:* www.chromacademy.com/infrared-training.html

**Fundamental LC–MS**  
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*Website:* www.chromacademy.com/mass-spec-training.html

**Overview of Solid-Phase Extraction**  
On-line training from CHROMacademy  
*Website:* www.chromacademy.com/sample-prep-training.html

**Solid-Phase Extraction**  
Onsite training  
*Website:* www.crawfordscientific.com/training-consultancy/other-chromatography-courses/solid-phase-extraction

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Please send your event and training course information to Kate Jones  
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Event News

11–13 September 2019
The 12th Balton Symposium on High-Performance Separation Methods
Siófek, Hungary
E-mail: felinger@ttk.pte.hu
Website: www.balaton.mett.hu

29 September–1 October 2019
SFC 2019
Philadelphia, Pennsylvania, USA
E-mail: register@greenchemistrygroup.org
Website: www.greenchemistrygroup.org/current-conference/sfc2019

21–23 October 2019
Solutions and Workflows in (Environmental) Molecular Screening and Analysis (SWEMSA 2019)
Erding, Germany
E-mail: info@swemsa.eu
Website: www.swemsa.eu

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