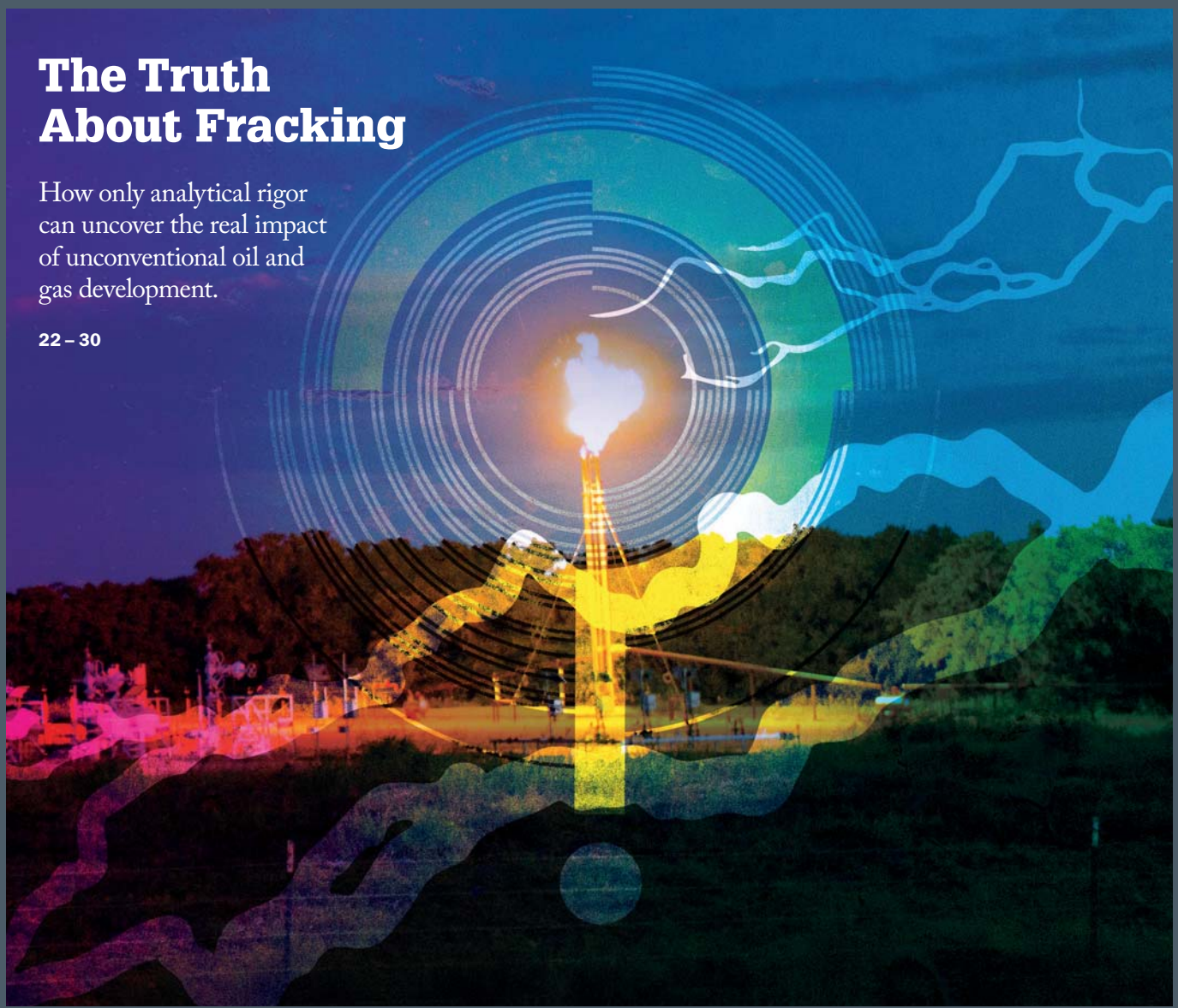
SEPTEMBER 2017 # 56

# the Analytical Scientist™





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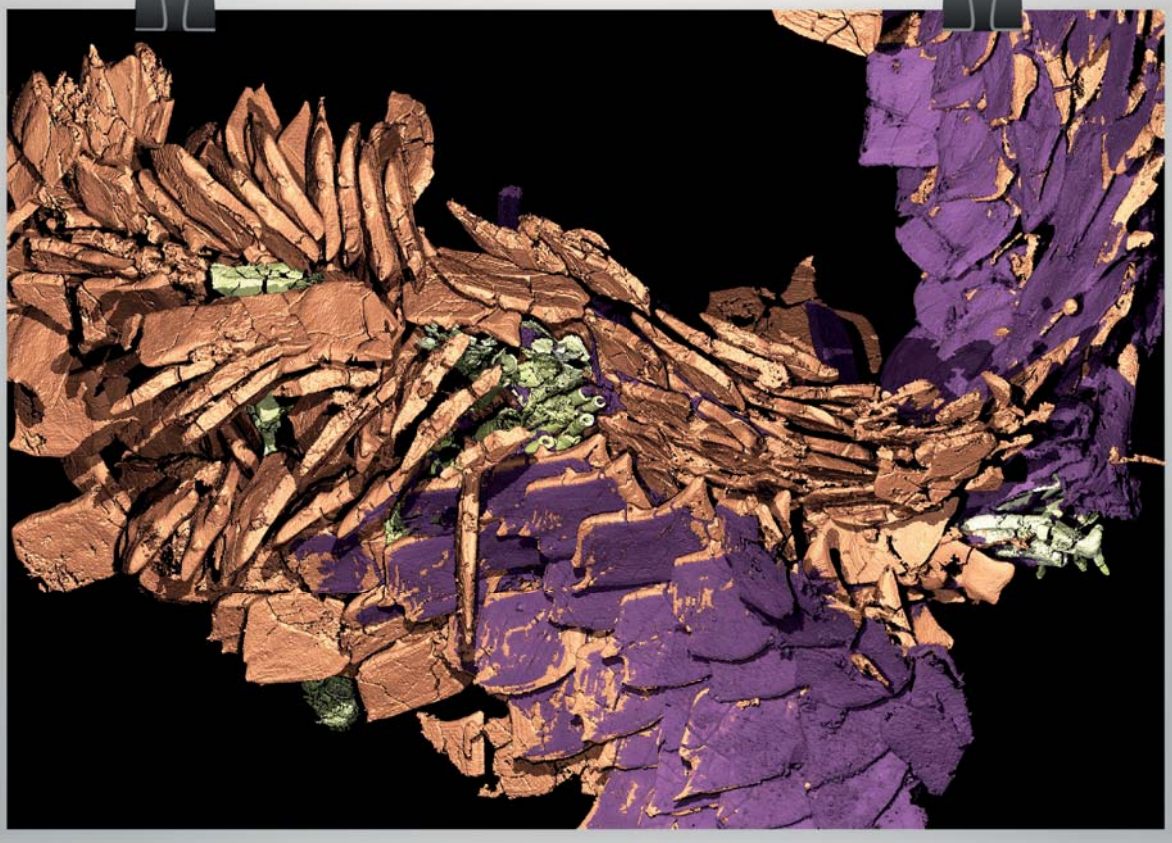
# Image of the Month



*Looking Out for Number Two*

Those of a delicate constitution, put down your lunch: you're looking at fossil feces. Known as coprolites, these fossilized food remains can provide insights into "ancient trophic relations" (1) – prehistoric food chains. Using propagation phase-contrast synchrotron microtomography (PPC-SRμCT), researchers from France and Sweden segmented coprolites into 3D models, and discovered 230-million-year-old remains of articulated fish scales and lepidotrichia (segmented fin rays) in what is thought to be the fossilized droppings of a lungfish.

*Reference: M Qvarnström et al., "Synchrotron phase-contrast microtomography of coprolites generates novel palaeobiological data", Scientific Reports, 7 (2017).*

Would you like your photo featured in Image of the Month? Send it to charlotte.barker@texerepublishing.com

# Contents




## On The Cover

*An unconventional oil padsite flaring natural gas in the Eagle Ford shale of south Texas.*

## Upfront






the Analytical Scientist

ISSUE 56 - SEPTEMBER 2017





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# Doing the Impossible...
*... for the love of humanity!*



A dinner table discussion about Hurricane Irma (24 people dead) and Mexico's 8.2 earthquake (90 people dead) and the resulting devastation culminated in a late-night movie: The Impossible – a portrayal of one family's experience of the 2004 Indian Ocean tsunami that ripped through the otherwise idyllic Kao Lak in Thailand.

Though contrived in parts - and dramatized where absolutely no additional drama was required - the filmmakers did succeed in two compelling aspects (the reason behind my friend's recommendation): i) depicting the horror of real-life disaster and desperation, and ii) showing how good (or not) people can be in times of crisis.

Certain (often subtle) moments really triggered my empathy chip. In particular, I was reminded of the Tōhoku earthquake and my concern for friends after a monster tsunami decimated Japan's northeast coast in 2011 (15,894 people dead and 2,562 missing, according to a National Police Agency report in 2015). But helicopter footage fails to capture the turmoil and tragedy unfolding under the ravaging water (unlike The Impossible).

As analytical scientists, you're used to dealing with numbers - how else could you quantify anything? And when it comes to humans - particularly those in far-flung lands - it's often easier to deal with the numbers that catalog victims of catastrophe, atrocity, disease or famine by not fully acknowledging that each unit represents a life, a family, and heartbreak. But clearly, we are not simply numbers.

It is almost impossible to fully protect people against natural disasters. But for preventable suffering, absurdly large numbers can spark outrage or, more productively, the strong desire to 'do something.' Why are half a million people (two thirds of them children) dying from malaria - a treatable disease - each year? Why are more than half of the people infected with HIV unaware of the fact? Those two questions motivated the first and second Humanity in Science Award-winning projects, respectively (1).

As analytical scientists, you have already been motivated to 'do something.' After all, (analytical) science is often driven by the desire to improve the safety of our drugs, food or environment - or to better understand, diagnose and treat disease.

The third Humanity in Science Award winning project will be announced and presented on October 2 in Berlin to coincide with KNAUER's 55-year anniversary; we're delighted to have KNAUER on board as partners for the 2017.

But what is humanity? Being compassionate? Being generous with our resources or skills? Helping people in need? Well, sometimes it also requires the vision to solve a problem that seems impossible.

**Rich Whitworth**
*Content Director*

*Reference*

1. *www.humanityinscienceaward.com*

# Upfront

*Reporting on research, personalities, policies and partnerships that are shaping analytical science.*

*We welcome information on interesting collaborations or research that has really caught your eye, in a good or bad way. Email: charlotte.barker@texerepublishing.com*

## Writing Off Cancer

**When it comes to identifying cancerous tissue, is the "MasSpec Pen" mightier than the iKnife?**

Meet the MasSpec Pen, a handheld mass spectrometry device with the potential to speed up accurate and intraoperative diagnosis of human cancer. The pen – which releases a water droplet onto suspected cancer tissue before drawing it back up for chemical analysis – was able to predict cancer with high sensitivity (96.4 percent), specificity (96.2 percent), and an overall accuracy of 96.3 percent (1).

Finding and removing the edges of cancerous tissue by sight alone is a particular challenge for surgeons, and successful resection of all the cancerous tissue clearly has huge health implications for the patient. The resulting demand for precise, accurate and rapid detection has already inspired one similar device: the electrosurgical iKnife, which uses rapid evaporative ionization mass spectrometry (REIMS; see tas.txp.to/0215/PrecisionMedicine).

The MasSpec Pen was conceived two years ago by Livia Schiavinato Eberlin, Assistant Professor, Department of Chemistry, University of Texas at Austin (notably, one of The Analytical Scientist's Top 40 Under 40: tas.txp.to/0714/40Under40) – but for this small, yet seemingly mighty technology, it is only the beginning.

"We are going to further validate the technology in my lab with larger sample sets and expand to other cancer types – then we'll start testing in surgeries with our colleagues in the Texas Medical Center to compare our results with current results from clinical practice," says Eberlin. "Next we should expand to larger clinical trials to really prove that the technology can improve surgical treatment and patient care." Eberlin and team hope to be able to trial the device during operations within the next 12 months.

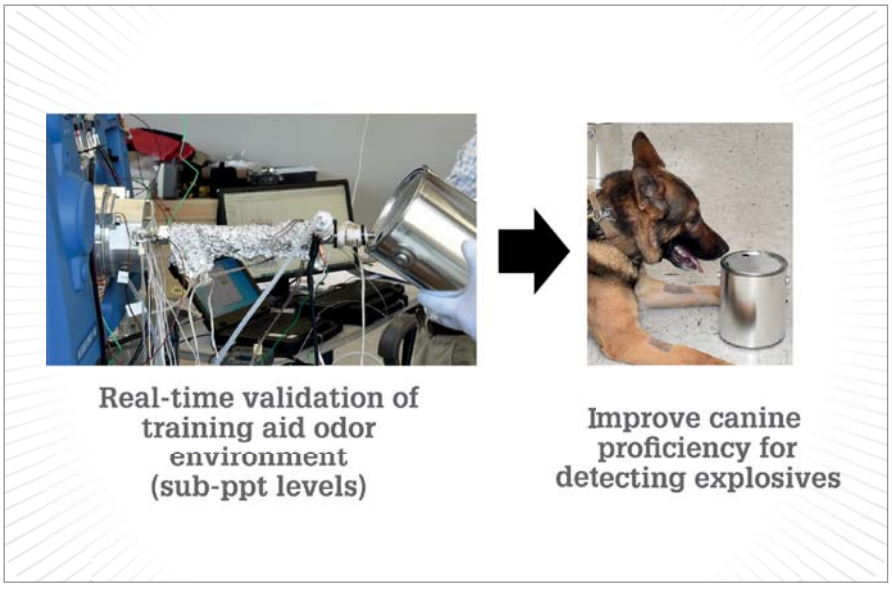
Eberlin says it is very rewarding to work on a project with such high potential impact. "Since working with R. Graham Cooks during my PhD, the last 10 years of my career have been dedicated to translational and clinical research, and I am excited about the recent development of the MasSpec Pen," she says. "I am very passionate about the field, and specifically about developing mass spectrometry technology that can make a real difference in clinical practice. My amazing research team and I have been working extremely hard on this project. It is amazing to see what they have accomplished so quickly!" *JC*

*Reference*

1. *J Zhang et al., "Nondestructive tissue analysis for ex vivo and in vivo cancer diagnosis using a handheld mass spectrometry system", Sci Transl Med, 9, eaan3968 (2017).*

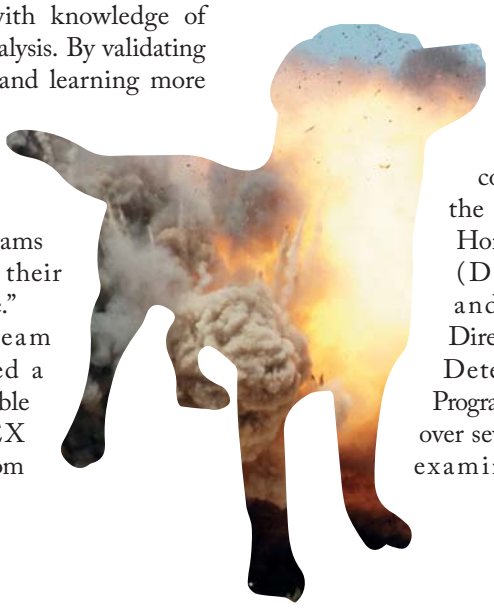
# Paw of the Law

**New MS technology could help canines become better "chemical sensors" for explosive detection**




When it comes to the detection of explosives, canine teams are still considered the gold standard (1). However, detecting explosives in the ambient air can be challenging for man's best friend (as well as instrumentation) – especially because national security measures necessitate real-time and high sensitivity detection of a large range of chemical classes and concentrations. "Like any thorough scientist, canine trainers would like to validate vapor presentation to the canine," says Ta-Hsuan Ong, lead researcher of a recent MIT study into canine bomb detection (1). So how can we teach these dogs some new tricks?

"Knowledge gained about the vapor environment can help with choosing the right training aids. Our new vapor-analysis mass spectrometry method provides trainers with additional information on vapor presence, concentration, and identity," says Ong. "Our goal is to iteratively improve canine training best practices by combining the experience of canine teams with knowledge of instrument vapor analysis. By validating vapor presentation and learning more about the canine training vapor environment, we can improve how efficiently canine teams are maintained at their optimal performance."



Ong and his team from MIT coupled a commercially available mass spec (SCIEX QTRAP) to a custom ionization source able to switch between secondary electrospray ionization (SESI) and dielectric barrier discharge ionization (DBDI), both of which offer detection limits of nine explosives (2,4-dinitrotoluene [2,4-DNT], 2,6-dinitrotoluene [2,6-DNT], 2,4,6-trinitrotoluene [TNT], nitroglycerin, 1,3,5-trinitroperhydro-1,3,5-triazine [RDX], pentaerythritol tetranitrate [PETN], triacetone triperoxide [TATP], hexamethylene triperoxide diamine [HMTD], and cyclohexanone) down to the parts-per-trillion to parts-per-quadrillion range by volume – comparable with or better than canines.

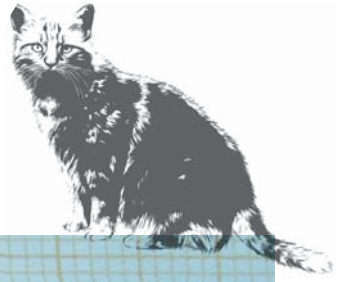
The custom source and MS combo was commissioned by the Department of Homeland Security (DHS) Science and Technology Directorate's (S&T) Detection Canine Program and developed over several years. "We examined different stages of vapor transfer and ionization from the environment into the mass spectrometer, using a combination of fluid dynamic simulations and experimental measurements," Ong says. "Method development was additionally driven by conversing with canine trainers about what material they were interested in detecting."

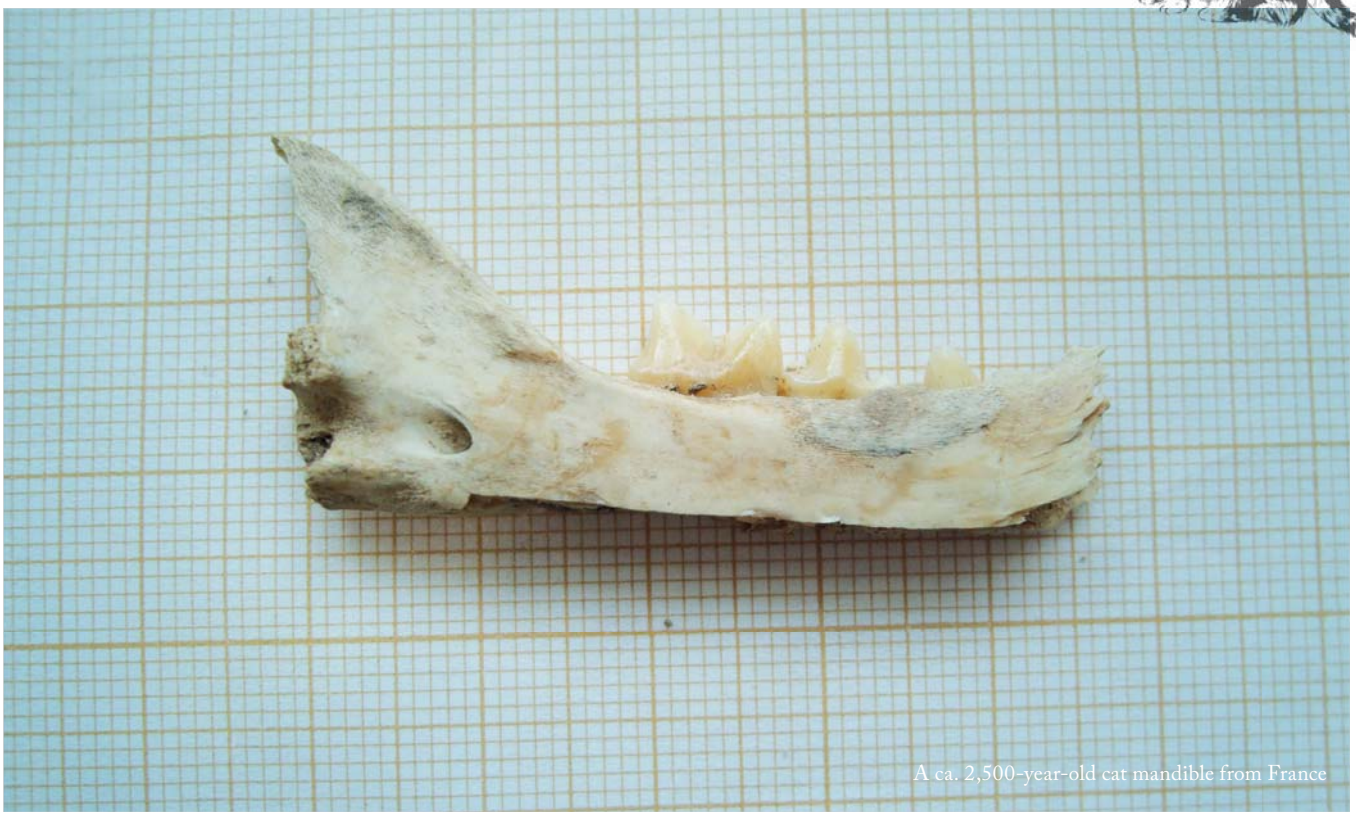
The MIT Lincoln Laboratory (LL) has been developing technology in support of national security since the 1950s, according to Ong. "With the threat from improvised explosive devices (IEDs) increasing over the past 10–15 years, MIT LL has been begun to develop a wide range of technologies to minimize the threats they pose," he explains.

The team are now working with Don Roberts, who leads the DHS S&T Canine Program, to work out how best to use the system to help the trainers and their four-legged companions successfully sniff out explosives. *JC*

*Reference*

1. *T-H Ong et al., "Use of mass spectrometric vapor analysis to improve canine explosive detection efficiency", Anal Chem, 89, 6482–6490 (2017).*





A ca. 2,500-year-old cat mandible from France

# Good Mews Traveled Fast

## Pussycat, pussycat, where have you been? All over the Ancient World, apparently

Work in the high containment laboratory

The Egyptians' love of cats is well known – and well reflected in their iconography. Now, for the first time, a large team has used a paleogenetic approach using ancient DNA analysis and direct accelerator mass spectrometry (AMS) to better comprehend the poorly understood process of feline domestication – and confirmed the role the Egyptians played.

Eva-Maria Geigl (Research Director at the National Research Center CNRS Jacques Monod Institute, Paris, France) and Wim van Neer (a zooarchaeologist from the Royal Belgian Institute of Natural Sciences), have worked in the paleogenetics field for many years, retrieving DNA data from archeological samples discovered in the Fertile Crescent (Levant, northern Syria, southeast Anatolia,

Iraq and northern Iran) – the heart of the feline domestication zone. "DNA preservation correlates in part to temperature (it is less well preserved in hotter climates) – not only were the cat remains old, but they were not cold," says Geigl. "Cat bones are also small and fragile, and contain only a few small compact regions, if any, where DNA is preserved – so we knew this was going to be a challenging task!" Nevetheless, the team collected data from over 200 ancient samples from the Near East, Africa and Europe to get a global view of the cat domestication process.

Ancient DNA analysis is a painstaking process, Geigl explains. "When one extracts DNA from ancient remains, one ends up with very few, very degraded DNA molecules that need to be multiplied to be sequenced. In the past, this multiplication was done via PCR (polymerase chain reaction), which allowed us to multiply a given genetic locus but was prone to contamination by modern DNA that is difficult to detect." To overcome this, the team concentrated on the development of experimental methods (1) to eliminate modern, contaminating DNA molecules, before dating the samples using direct accelerator mass spectrometry.

They found that cats accompanied people on their journeys, from the Near East in prehistoric times and from Egypt in Classical times, slowly conquering the Ancient world. "Over time the original distribution of the mitochondrial lineages that characterize the various wildcat populations started to change," says Geigl. "They crossed the Bosphorus (a waterway in northwestern Turkey) and started to colonize Europe. The cat could not have swum through the Bosphorus alone, so this told us that it was transported by humans."

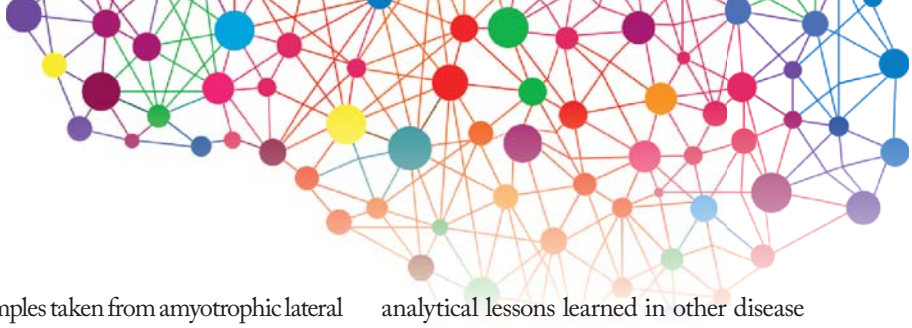
Half the samples analyzed carried a different lineage they had not seen before elsewhere, showing that the Egyptian cat became very popular during this period. "It suggests that during the long relationship between humans and cats in Egypt, the cats acquired new features interesting to humans that other cats from Anatolia and the Levant did not have," says Geigl. The team found the same Egyptian lineage in samples from roughly the 8th century in a Viking port in the Baltic Sea, confirming the growing worldwide popularity of this cat.

The distinctive animal was not the only feline to go on a "mews cruise," says Geigl. "The mitochondrial signature of the Indian wildcat was found in a sample from the Roman port in Egypt (the Red Sea) that traded with India. We believe it further supports the theory that cats were on ships, probably to get rid of rodents that destroyed the food supply and navigation equipment, such as ropes, and therefore spread across the world."

In the future, the team hope to analyze the nuclear genomes in ancient cat remains to uncover the whole story of taming, domestication and admixture with wild cats. *JC*

*Reference*

1. *Ottoni, C. et al. "The palaeogenetics of cat dispersal in the ancient world", Nat. Ecol. Evol. 1, (2017).*



# Spinal Tap

## Metal speciation in cerebrospinal fluid may bring new understanding of neurodegenerative diseases

Debilitating and often incurable, neurodegenerative diseases could affect over 12 million Americans by 2030 (1). Finding treatments – or, even better, cures – for these conditions is a high priority. But first, we need to understand them.

High levels of metal ions in the cerebrospinal fluid (CSF) are currently thought to play a key role in protein misfolding – a hallmark of neurogenerative disorders – so a multinational team of researchers developed a method for simultaneous redox speciation of iron (II/III), manganese (II/III), and copper (I/II). Based on strong cation exchange chromatography and inductively coupled plasma sector field mass spectrometry (ICP-sf-MS), the new method was optimized and tested using real CSF samples taken from amyotrophic lateral sclerosis (ALS) patients and neurologically healthy controls (2).

"The underlying hypothesis of our studies is that, unlike cycling body fluids (for example, blood or serum) or excretory media, the CSF is in direct contact with the brain parenchyma and brain extracellular fluid," says Nikolay Solovyev from St. Petersburg State University. "So, slight changes of trace element speciation caused by exposure or redox dis-homeostasis related to neurological pathology would be more clearly reflected in the CSF than in other matrices." Less cerebrally put: higher levels of the primary species of interest detected in CSF could act as "red flags" for various neurodegenerative diseases (3).

Next, Solovyev and the team plan to complement their metallomics studies on ALS with non-specific metabolomics research to see how metal species interact with metabolites in the CSF, with the ultimate aim of discovering candidate biomarkers.

Solovyev and the team want to apply analytical lessons learned in other disease areas, and will soon begin an investigation into copper speciation in Wilson's disease as part of a biomarker research project alongside new partners from Guildford, UK: "Here, we would like to improve the current approaches for ceruloplasmin determination using hyphenated techniques – and implement this into clinical chemistry. I would like to thank my colleagues from Germany, Italy and UK for our collaborations." *JC*

*References*

1. *Harvard NeuroDiscovery Center, "The challenge of neurodegenerative diseases". Available at: http://bit.ly/2soDGmD. Accessed July 7, 2017.*
2. *N Solovyev et al., "Redox speciation of iron, manganese, and copper in cerebrospinal fluid by strong cation exchange chromatography–sector field inductively coupled plasma mass spectrometry", Anal Chim Acta, 973, 25–33 (2017).*
3. *B Michalke et al., "The importance of speciation analysis in neurodegeneration research", TrAC Trends Anal. Chem., doi: 10.1016/j.trac.2017.08.008*

# Discoveries, Diagnostics and Dissolution

## What's new in business?

In our regular column, we partner with www.mass-spec-capital.com to let you know what's going on in the business world of analytical science. This month, there are a number of large-scale acquisitions, and a Merck Award goes to Francesco Ricci from the University of Rome, for the development of innovative DNA-based nanodevices.

### Products

- bioMérieux: FDA expands pathogen identification on VITEK MS

### Investment & acquisitions

- Metabolon acquires Metabolomic Discoveries GmbH
- Thermo Fisher Scientific completes $7.2b acquisition of Patheon
- Merck to acquire Ontario-based Natrix Separations
- Eurofins acquires two Japanese analytical firms
- CDPQ to acquire significant minority stake in Sebia
- Fluidigm: $30m common stock in at-the-market equity offering
- Eurofins Scientific announces acquisition of DiscoverX
- Sysmex and bioMérieux to dissolve their joint venture

### Collaborations

- Fluidigm licenses CFTR NGS Assay from Baylor Genetics
- Biotecon Diagnostics to sell Bruker MALDI-TOF MS Systems
- SpectralWorks & Mestrelab: mutual reseller agreement

### People

- Concept Life Sciences appoints John Handley as COO
- Merck KGaA announces board changes

### Organizations

- Merck opens its first Customer Food Safety Studio in Bellevue, WA, USA

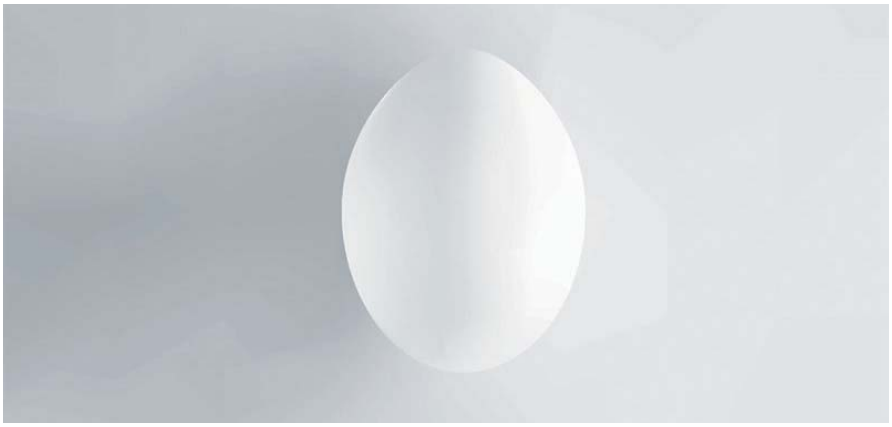
### Other

- Heinrich Emanuel Merck Award goes to Francesco Ricci

*For links to original press releases and more business news, visit the online version of this article at: tas.txp.to/0917/BUSINESS*

# Eggs-istential Crisis

## Pesticide found in thousands of Dutch eggs



Millions of eggs in 15 European countries have been removed from sale after elevated levels of Fipronil were detected. EU regulations state the maximum residue limit for Fipronil is 0.005 mg/kg – but some eggs were found to contains values of over 0.72 mg/kg.

Michael Nielen (Principal Scientist, Department of Agrotechnology and Food Sciences, Wageningen University and Research, Netherlands), believes a problem of this size underlines the need for portable, easy-to-use analytical instrumentation: "Given the scale of the scandal, the availability of on-site food analysis, such as portable MS/MS, would potentially speed-up risk management by food safety agencies, while reducing economic loss and restoring consumer confidence." Read more about the potential of handheld food analyzers on page 32.

The Netherlands food safety agency are currently believed to be carrying out spot checks on poultry farms (using LC/MS/MS) to ascertain whether chicken meat has also been contaminated. *JC*

# In My View

*In this opinion section, experts from across the world share a single strongly-held view or key idea.*

*Submissions are welcome. Articles should be short, focused, personal and passionate, and may deal with any aspect of analytical science. They can be up to 600 words in length and written in the first person.*

*Contact the editors at edit@texerepublishing.com*

## Testing the Boundaries

**Are you compliant with the new guidelines for elemental impurities? There are only six months left to get up to speed.**

*By Sarah James, Principal Scientist, CMC Analytical Services at LGC, UK.*

In June 2016, the FDA announced new draft guidance on reducing elemental impurities in drug products. Elemental impurities can make their way into a drug product from various points in manufacturing processes – and in some cases can be a risk to patients. The aim of the guidance is to help manufacturers of both new and generic small-molecule drugs to comply with recent standards introduced by the International Council for Harmonization (ICH) and US Pharmacopeial Convention (USP). These standards, which are established in USP General Chapters <232> Elemental Impurities – Limits, and <233> Elemental Impurities – Procedures, as well as ICH Q3D – Guideline for Elemental Impurities, come into full effect at the start of 2018 and place drug elemental impurities into various new hazard categories based on their toxicity (permitted daily exposure [PDE]) and likelihood of occurrence in the drug product, which is derived from a number of factors including probability of use in pharmaceutical processes, probability of being a co-isolated impurity with other elemental impurities in materials used in pharmaceutical processes, and the observed natural abundance of the element.

To comply with the new guidelines, companies will need to carry out a detailed risk assessment of their materials using the new categories. For non-experts, the subject of elemental impurities can be daunting; extensive expertise is needed to effectively characterize elemental impurities, including the development and validation of appropriate assays. Traditionally, wet chemical tests have been used for the determination of heavy metals in drug products but, in my view, inductively coupled plasma-optical emission spectroscopy (ICP-OES) and inductively coupled plasma-mass spectroscopy (ICP-MS) are much better approaches since they offer improved elemental specificity, accuracy, and sensitivity – as well as the added confidence that comes from targeted quantitative data. Not only are these techniques well placed to ensure that materials meet the new compliance criteria, they are also already well used in the industry.

But is the industry ready for the new guidelines and the increased use of these techniques? I am not so sure. The typical remit of today's pharmaceutical quality control laboratories does not normally include delivery of large volumes of ICP-OES/ICP-MS drug product testing. To succeed, experience and knowledge will be key. Scientists will need to understand how to develop both limit and quantitative test methodologies for a wide range of sample matrices, as well as being able to effectively use specialized sample preparation techniques and digestion regimes. Metal speciation is also challenging and requires the use of either intricate targeted sample preparation to solubilize only the desired species or chromatographic separation, followed by ICP-MS as an ion detector. The latter approach is becoming more common within inorganic laboratories as techniques such as HPLC-ICP-MS become more affordable and accessible.

Companies will need to implement a control strategy to ensure that their drug products meet the new guidelines, which may range from purely paper-based risk assessments (if manufacturing controls and existing elemental impurity data are sufficient) to analytical screening of complete product portfolios. Where initial risk assessments highlight potential control issues, targeted analysis of specific products or components may be necessary. Screening involves examining at least 24 elemental impurities at 30 percent PDE in multiple dosage forms with multiple maximum daily doses.

I believe the risk of elemental impurities being present in the majority of final products is generally low because of existing manufacturing and supply chain controls. However, providing sufficient evidence for this within an ICH Q3D risk assessment without the use of screening data can be difficult – especially given the lack of existing elemental impurity data for many product components. In higher risk scenarios – for example where the patient is exposed to exceptionally high doses, or where products contain significant quantities of natural, mined excipients – provision of adequate evidence is even more important. The finalization of ICH Q3D, and the associated implementation of USP <232> and <233>, has been a long drawn out process. Some in the industry have been slow to react to the forthcoming changes and many others still do not understand the guideline's requirements. But we're now over half way through 2017 and the 2018 deadline is looming...

# Calling All Mentors

**Academics and industrial chemists: share your experience and advice with young scientists. We must motivate more students to enter the analytical sciences.**

*By Charles Lucy, Professor Emeritus and 3M National Teaching Fellow at the University of Alberta, Canada.*

It is the start of a new school year here at the University of Alberta. My office window rattles with the thumping music that accompanies the herds of eager new students wandering our campus. Chatting with students, I learn of their career plans to be a doctor, engineer... rarely a chemist. And never an analytical scientist. As I wipe the tears from my eyes, I ask, "Why don't students want to be analytical scientists?"

When people choose a particular university degree, the four driving forces are: career motivation, intrinsic interest in the subject, the opportunity to help others, and the desire to get an easy degree (1). Those choosing medicine are motivated both by the desire to help others and the belief that there are careers in the field. Students enter engineering based on its career opportunities, while their intrinsic interest in the field is sadly low. Science students are driven by interest in their field, while the possibility of a science career has not factored into their decision. Not surprisingly, they don't perceive science as easy.

So why do I bring this up? Because there is a high demand for analytical chemists in industry. Analytical chemistry is the largest category of employment for chemistry in the United States (2) and many other countries. Knowledge of career options would motivate more students to enter the field. Unfortunately, most academic analytical chemists, such as myself, have little industrial experience, so are ill equipped to advise students about careers in the analytical sciences. That is why I am calling on you!

At the University of Alberta we recently established a seminar course that models some of the ways that practicing analytical scientists can make a big impact on students and their career plans (3, 4). The primary component is a weekly one-hour seminar by local industrial and government chemists (often our alumni) who share their career paths, briefly introduce their company and laboratories, talk about the science they are working on, and discuss career opportunities in their industry. Students come loaded with many questions, and the speakers are eager to share their experiences and their advice.

The course also includes tours of local industry, which are always a highlight for the students, who are amazed both at the industrial scale, and the discovery that there are chemistry jobs in their local area!

Our course culminates in a mock interview. Practicing chemists provide a job ad typical of an entry-level chemistry position in their company, and students write a cover letter and resume tailored for that position. The industrial chemists come to interview the student in their company's typical interview style and then provide confidential feedback. The students find this experience invaluable and the interviewers enjoy it, too. Some companies also do recruitment interviews based on the same job ads. Last year, about a dozen students received job offers.

But it is the informational interview that has been most influential for students – and it requires little time or effort from the professional chemist (5, 6). The student meets with someone with industrial experience to learn about the

industry, the company, and about careers in the field. We also have the students do informational interviews with returning industrial internship students, with graduate students who have industrial experience, and, most valuably, with local alumni. Such interviews can be as simple as a conversation over coffee, but are nonetheless invaluable to the student.

In conclusion, I encourage academics to reach out to their alumni and their local industrial colleagues to meet with their students. Similarly, I encourage industrial chemists to reach out to your alma mater or to your local college, and offer to share your experience. These "sharings" can be as simple as a chat with a class or as formal as a tour of a lab. Academics, rest assured that your request will be met with enthusiasm – I have yet to have an alumnus turn me down. Analytical scientists, rest assured that what you do is cool, and that you work with some really awesome toys. Students will be fascinated by what you do. And seeing that there are interesting and important jobs in the analytical sciences will encourage students to consider a career in the field.

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# One App to Rule Them All

**Is SAP the only system you need to operate your Lab? A Lord of the Rings Parody.**

*By Geoff Turnbull, Delivery Manager, CSols, Inc, Newark, Delaware, USA.*

One by one the Applications of the Enterprise fell to the power of SAPron. Some resisted; a last alliance of Lab Analysts, Product Vendors and Research Scientists fought for the freedom of The Lab. But the power of the SAPron could not be undone. The promises of reduced TCO and "One application to rule them all" corrupted the will of men.

SAPron's quest for dominion had extended from the earthly Enterprise domain into the realm of the ether; Ariba, Concur, and Fieldglass all swore allegiance to SAPron and quickly succumbed to the power of the one app. Under the control of SAPron, they spread its hold – the whole world of commerce was falling into SAPron's grasp.

For many an age, The Lab continued as before, blissfully ignorant of these new alliances, confident that they were insignificant enough not to be seen by the eye of SAPron. Despite predicting the demise of the kingdoms of The Lab for some time, SAPron had seemingly made few inroads into the realms of The Lab. Complacency set in and the rising storm clouds were ignored.

But unseen and unnoticed by many, SAPron had taken over seemingly innocuous elements of their realm. Quality assurance functions, specification management, and instrument management applications were no longer under the sole purview of The Lab. They were becoming bound to the one app under the guidance of QM. SAPron promised that he would integrate the power of the one app with those of The Lab, through the QM IDI-interface. It appeared that SAPron was no longer seeking total domination; rather a means of coexistence.

SAPron's influence and the power of the one app had reached the highest levels in some kingdoms of The Lab. Some leaders were convinced that the one app would be enough to operate their Labs. However, their attempts to implement with QM and realize the promises of lower TCO produced mixed results. A level of success was achieved in low volume operations that performed simple analytical testing requiring no automation, but in medium-volume operations where there was a need to automate some of the routine tasks, additional applications were required. Applications that handled simple instrument integration and lab specific processing, such as LIMSLink, were often favored to fill this role. Despite attempts by SAPron to meet their needs, high-volume operations performing complex analytical testing continued the use of LIMS, which remained the only truly viable solution.

For now, SAPron appeared to be in retreat, with only those performing the simplest of operations, under the power of the one app. Was SAPron's battle for The Lab over?

Through these skirmishes the need for coexistence between The Lab and SAPron had been established. But coexistence itself brought many challenges. Who should be the True Master of certain data, such as product and test specifications? Does QM need all testing results, final results, or maybe just a pass/fail indicator? Where should raw data be stored?

While these terms were being negotiated, SAPron was actively supporting new

and improved terms of integration. He introduced XI to facilitate the exchange of information between the One App and other apps within the kingdom. Pleased with the accomplishments of XI, SAPron bestowed upon him the new name of PI. The people of The Lab were encouraged to expand their Lab apps and work with, rather than fear, the power of the One App. Perhaps coexistence could be realized after all…

However, building communication channels was not all that SAPron was doing. Unbeknownst to The Lab, SAPron had tasked SAPuman with the proliferation of more granular Lab functionality within QM, and the creation of more powerful functionality that could support even the most complex Lab needs. QM had once again been enhanced and was ready to be unleashed.

The Lab sought out alliances of their own. Overlooked by SAPron, the Research Scientists – the oldest and possibly the wisest inhabitants of The Lab – further strengthened their resistance with their ELN solutions. The unlikely alliance meant the resistance could now offer integrated Lab informatics platforms that could be used from research and discovery through to development and manufacturing.

And nor were the Lab Product Vendors idle. Though the traditional LIMS was adept at sample management, it did not adequately address test execution. A new application, LES, was created to solve this problem. Surely the One App could not provide such functionality! Certain Lab Product Vendors also included SDMS into their integrated platforms, capturing, cataloging, and archiving data generated by instruments within The Lab in real time. SAPron may be ready for battle, but this time The Lab is prepared! What will be the outcome?

Without doubt the One App should be the Master, and should identify sources of all data pertinent to the supply chain within The Lab. But certain questions remain. What data is pertinent, and what is meant to bind them? Does bind mean assimilate or integrate?

The battle for dominion rages.

*Glossary*

*SAP: Enterprise software*

*QM-IDI interface: Inspection Data Interface in Quality Management*

*LIMS: Library information management systems*

*SAP XI: SAP exchange infrastructure, SAP's enterprise application integration (EAI) software*

*QM: Quality management*

*ELN: Electronic lab notebooks*

*LES: Logistics execution system*

*SDMS: Scientific data management system*

# Water, Water Everywhere

**Determination of $H_2O$ may be ubiquitous and appear relatively straightforward but, with increasingly strict regulations and the constant drive towards more accurate measurements, how confident are you in your results?**

In the summer of 2017, we surveyed readers about trends and challenges in water determination. Here, we share the results – and interview Honeywell's Michael Jeitziner for expert commentary.

The majority of survey respondents (86 percent) said that accurate measurement of water in their samples was very important or important (see Figure 1)... Accuracy is an analytical cornerstone, so this is in no way surprising. The development of the Hydranal™ range for Karl Fischer titration has always focused heavily on improving accuracy. To that end, Honeywell Research Chemicals recently became the first commercial supplier of certified reference materials (CRMs) for Karl Fischer titration to gain so-called Double Accreditation, meaning that the new generation of standards is produced and certified under ISO Guide 34 in addition to ISO/IEC 17025. Double accreditation means not only that researchers can comply with the strictest regulatory requirements, but also that they gain access to highly accurate results. Our decision to move to CRMs is reflected by the needs and demands of our users – two thirds of survey respondents need (32 percent) or prefer (34 percent) CRMs for Karl Fischer titration (see Figure 2).

Two thirds of survey respondents identified measurement reliability as a major challenge in water determination. Is this surprising?

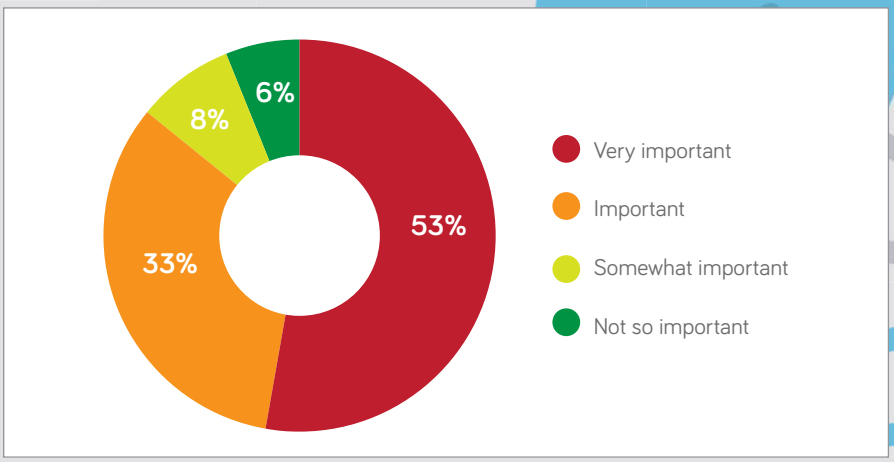



Figure 1. How important is the accurate measurement of water in your sample to your work/research?

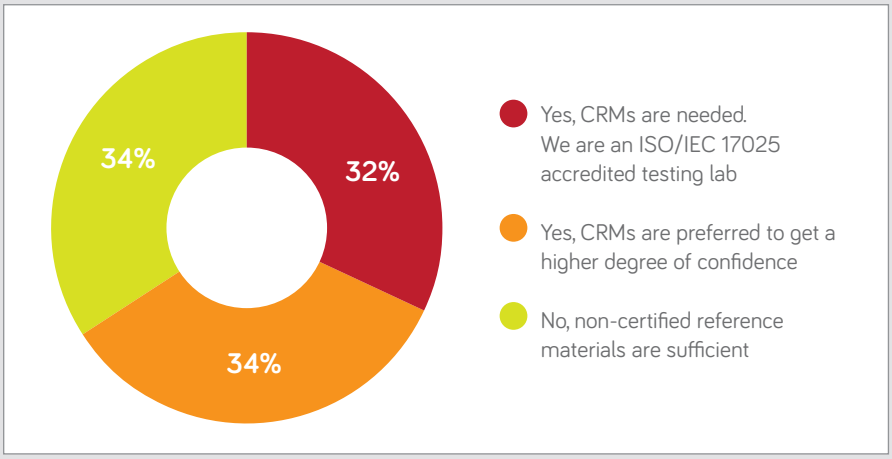



Figure 2. Certified reference material demand. (Survey question: Do you buy certified reference materials (CRMs) for Karl Fischer titration?)

I think reliability goes hand in hand with accuracy. And certainly, the boost in quality gained by the use of CRMs helps with reliability of results. But I would also point to the need for regular calibration – as with any measurement – to ensure that variance is kept to a minimum.

I note one survey respondent who indicates that they use homemade Karl Fischer reagents. And though that may save money (but not time), accuracy and reliability would be seriously questionable! I can say, without bias, that it's a bad idea. But I suspect they were also one of the few people to select that an accurate measurement is "Not so important"!

Over two thirds of survey respondents (69 percent) require application or technical support (see Figure 3). How does Honeywell bridge the knowledge gap?

At Honeywell, we consider technical and application support to be key differentiators – and that's because, once again, we want to meet the demands of our customers, as reflected in the survey results. We have an application laboratory that has produced over 700 reports covering a wide range of requests from customers, and covering diverse sample types. And our dedicated

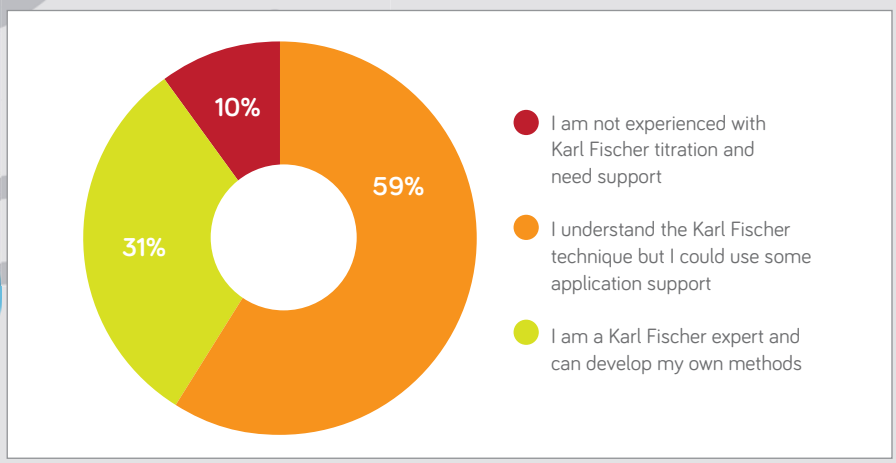



Figure 3. Karl Fischer expertise. (Survey question: in which of the following categories would you place yourself?)

application chemist will continue to drive that number higher. Unusually, our customers can contact our laboratory with technical or application questions directly, rather than going through a general technical service department – and that means users receive advice directly from seasoned Karl Fischer experts.

We also hold open Karl Fischer seminars (and webinars) as well as onsite seminars for companies to build skills in water determination.

The majority of survey respondents were from the pharma (39 percent), chemical (16 percent), and food & beverage (13 percent) industries, but a diverse range of market areas – from aerosol packaging to fertilizers to petrochemicals – were represented. What market trends have you noticed over the last 15 years?

It's not surprising that Karl Fischer titration has great utility across many different markets (a fact that's reflected in our Hydranal user data) – after all, as the title suggests, water is everywhere! It's also not surprising that the pharmaceutical industry tops the survey results, driven as it is by extensive regulation (once again, this is reflected in Hydranal use). In terms of trends, regulations have notably become stricter across the globe, and that has driven the need for more accurate analysis – especially in the pharma industry, but also elsewhere. In the food industry, quality is the main driver; water content affects the physical properties of products (the melting point of chocolate or the solubility of instant coffee, for example) and, therefore, product consistency, and it also has an impact on microbiological stability.

Another trend that we've noticed across the board is the demand for safer reagents – and 60 percent of survey respondents considered it an important element of a comprehensive Karl Fischer titration solution. We've always considered safety – both from an environmental and laboratory point of view – a high priority, and we continue to develop products that are less toxic.

Finally, what, in your opinion, are the three most important considerations when it comes to Karl Fischer titration?

First, choose a high quality product – it is the route to faster titration, higher lot-to-lot consistency, and lower toxicity or improved safety. Second, look for a company that offers a complete solution to ensure that quality exists across all reagents and standards. Third, don't forget that you may need application or technical support – something that really stands out in the survey results.

## Honeywell's Hydranal

Michael Jeitziner – with a degree in physical and analytical chemistry – has been responsible for Hydranal in various functions for the last 15 years, first as a senior product manager at Sigma-Aldrich and latterly as global marketing manager at Sigma-Aldrich and Honeywell.

Jeitziner says, "I now oversee the Hydranal team in our Center of Excellence laboratory, so I'm still closely following the Hydranal story!"

For those unaware of the acquisition landscape of the past few years (though it was news that was difficult to miss at the time), Merck KGaA completed its $17 billion acquisition of Sigma-Aldrich in November 2015. Approval from the European Commission came with a number of antitrust caveats. "The acquisition was only approved on the basis that part of Sigma-Aldrich's business (inorganics and solvents) was sold, including a number of brands and trademarks. In short, Hydranal – the first second-generation Karl Fischer solution – is now brought to you by Honeywell," concludes Jeitziner, putting an end to any confusion. He is also keen to point out that the entire Hydranal team, including quality control and application chemists – with all their extensive expertise – moved across to Honeywell along with the product range.

*Discover more about Hydranal: www.lab-honeywell.com/products/featured-hydranal*
*Reach out to the Hydranal Center of Excellence team: www.lab-honeywell.com/hydranal-form*

# THE TRUTH ABOUT FRACKING

The use of hydraulic fracturing – fracking – to extract natural oil and gas has become a politically charged topic. As analytical chemists, our lab at the University of Texas at Arlington aims to inject some much-needed objectivity into the debate.

*By Doug Carlton Jr.*

In recent years, the US has seen a boom in unconventional oil and gas development (UD), including hydraulic fracturing, to extract oil and gas. Energy companies claim that it is safe, clean, and necessary if the US wants to ensure essential power supplies in the coming decades. However, environmental activists have raised concerns that fracking is contaminating local water and air.

Imagine you are a landowner in a rural community. An energy company representative comes to you and explains that your land contains oil or gas, and that you could be making "money for nothing". You sign the contract, thinking of how the money could benefit your family. Months later, dozens of heavy tractor trailers begin rumbling through narrow rural roads; the landscape and community begins to change. Change brings about uncertainty, which often leads to doubt. The unease is further fueled by a raft of conflicting information and propaganda online. You find yourself reading a forwarded email from your grandmother, with a picture of someone lighting their well water on fire, while in the background an American Petroleum Institute commercial booms "This ain't your daddy's oil" (1). During these confusing times, a health, environmental, or lifestyle change occurs and our minds tend to go immediately to the new kid on the block – fracking. Could a mystery illness or a change in your well water be the result of that contract you signed all those months ago? The energy company says one thing, environmental groups say the opposite – who do you believe?

Our environmental research has been an attempt to combat this uncertainty through objective science. As an academic research lab with a primary expertise in analytical chemistry, we felt we had a chance to investigate and communicate in a manner that other labs or government agencies struggled with.

## Tools of the trade

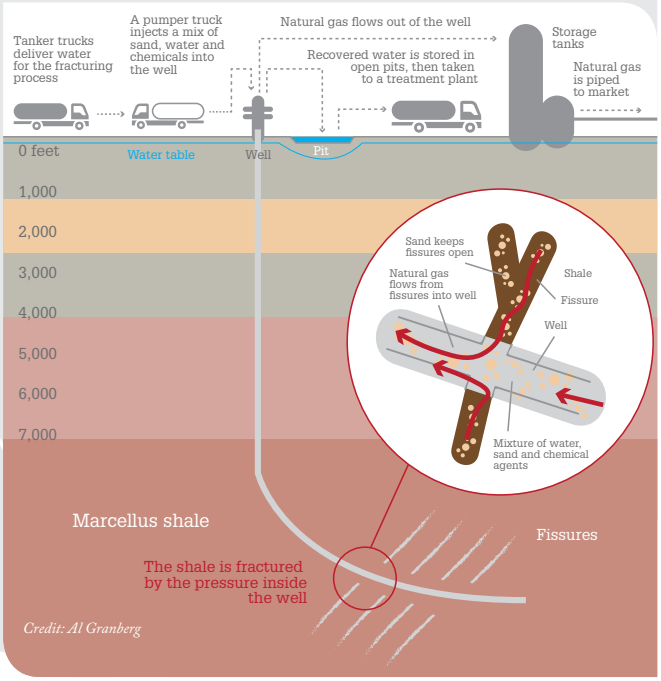
In the Spring of 2011, a couple of Dallas-Fort Worth area scientists walked into Kevin Schug's office at the University of Texas at Arlington (UTA). Zacariah Hildenbrand (then a postdoc and now at Inform Environmental, LLC) and Brian Fontenot (an independent consultant) had become curious about the effects of the rapid expansion of UD across this highly populated region. Their backgrounds in quantitative biology and biochemistry meant they had adequate design of experiment and participants, but no strong analytical support for the project. Kevin rarely says no to new research, especially research involving a gap in fundamental knowledge (or new toys!). As the only graduate student in Kevin's lab with gas chromatography (GC) experience, it became my "little side project". Six years on, I'm full-time Project Manager of what is now known as the Collaborative Laboratories for Environmental Analysis and Remediation (CLEAR; see "Making it CLEAR" on page 29).

We soon found that many standard methods, like US Environmental Protection Agency (EPA) drinking water methods or toxicology panels, fall short in terms of covering the exotic and/or undisclosed nature of the chemicals used in UD. Testing methods for industrial practices are designed to look for known targets, whether aged diesel from spills or heavy metal emissions from coal and cement plants. Shale extraction environmental research is still in its infancy in the US and there is no set list of proven chemical indicators, malpractice or unsafe releases specific to unconventional drilling. Regulations are left to each state and typically consist of traditional metrics from the EPA, National Institute for Occupational Safety and Health (NIOSH), or Occupational Safety and Health Administration (OSHA). Many of these measurements are collected over an 8- or 24-hour period, which risks underestimating short-term, high-level exposures of gases like hydrogen sulfide or carbon disulfide.

There is a massive burden of proof placed upon researchers investigating indications of UD impact, which is why we use multiple complementary measurements to validate detections. For example, high chloride and bromide measurements within

## A Beginner's Guide to Fracking

Hydraulic fracturing, known as fracking, is a technique to extract natural gas or oil trapped in underground rock formations (e.g., shale gas). A large volume of water, mixed with solid particles (proppants) and chemicals, is injected at high pressure into a well to create cracks in the rock, releasing oil and gas. The particles (sand or aluminum oxide) in the mixture lodge in the fractures, holding them open. Horizontal drilling is often used to maximize the volume of rock reached.




Left to right: Flaring natural gas separated from oil, a common practice for this gas rather than capturing and selling. Collecting samples from a water well. Inspecting groundwater samples before HS-GCMS analysis.

## Unconventional Drilling: Impacts

With any large-scale industrial process, you expect changes in the immediate surroundings. However, the impacts experienced in areas of unconventional drilling have been much broader than many residents or experts anticipated.

The benefits to communities include an influx of tax revenue locally, increased sales of food and other commodities, and infrastructure upgrades. However, extraction is a multi-week, multi-stage operation with a localized increase of people and traffic, bringing noise pollution, increased vehicle emissions, damage to roads and an influx of temporary workers. Environmental impacts can include VOC emissions from equipment to store and move oil and gas (10,11), surface water impairment from waste water spills (12), and potentially impairment of groundwater (13), all of which can have negative health effects.

Many of the impacts, positive or negative, come with any petroleum recovery operation, but risks that are unique or exaggerated with hydraulic fracturing include spills of produced water (drilling wastewater surfacing while the well is producing oil or gas), silica dust, large quantities of chemicals being stored at each pad, and truck traffic hauling water pre- and/or post-injection. The disposal of the resulting waste water in injection wells is also thought to increase the risk of earthquakes.

Though much attention has been focused on water, one of the greatest concerns for me is air quality. Ever since the electron capture detector was developed, the scientific and regulatory communities have become privy to the gases in our atmosphere. If forced, people can drink bottled water or change how they use their land, but we cannot "ship in" fresh air. Technology already exists to mitigate emissions – remote methane monitors, flare scrubbers, silica dust containment, to name just a few – but currently all monitoring and capturing technologies are voluntary.

Last year we published an emissions study investigating BTEX emissions of the various equipment found on active pad sites, with the University of North Texas (10). A mobile mass spectrometer allowed us to directly tie emissions to a particular location or machine on a pad site and showed that emissions from a particular location were not ubiquitous to all the pad sites and could be reduced with machinery upgrades or alternatives. For example, $H_2S$ scrubbers powered with diesel fuel generated more BTEX emission than those using alcohol-based fuel. I hope studies like these will help regulators prioritize improvements that protect our most precious resource – the air we breathe.

Clockwise from top left: Collecting sludge from abandoned waste fluid pit. Two photos showing real-time analysis of BTEX vapor from groundwater using mobile MIMS. Abandoned waste fluid pit.

a groundwater sample should be associated with a higher conductivity, and dissolved gas in groundwater should pair with an elevated total organic carbon (TOC) value. Our conclusions are still firmer when we can measure changes over time. An example of this would be arsenic measurements we made over 13 months on a ranches in West Texas (6). One water well had a significant amount of arsenic, more than double that allowed by EPA drinking water standards. Had we relied on only one time point, we may have been led to focus on identifying the source of the arsenic in this one well, but analyzing the well over time showed us that arsenic levels did not fluctuate as drilling increased, so we could rule out UD as a factor for the arsenic levels.

## *Zooming in*

Our research began around 2011 with samples taken across large areas of the Barnett (2,3) and Eagle Ford (4,5) shales, which gave us a general idea of the water quality but could not provide the spatial resolution needed to identify localized areas of concern. At this early stage of UD research, we didn't know whether we were looking for widespread or localized impacts.

As we collected those initial samples, we began hearing accounts from landowners about perceived changes in the surroundings, environmental quality, or personal health. We were shown running well water on fire, bubbling puddles that never dry, home foundation issues, and even copies of death certificates across a neighborhood. It was then that we realized that conspiracy theorists (often ordinary people driven by desperation) keep great lab notebooks. These events seemed to be happening in localized areas, limited to a neighborhood or two. Since our shale-wide surveys did not observe uniform or systematic anomalies, we thought greater information might be obtained from sampling more targeted regions over extended timeframes.

Our first time-course study was conducted in west Texas, in the expanding Cline Shale of the Permian Basin. One of our Barnett

Top: Oil padsite in the Eagle Ford shale region. Bottom: Camera being lowered into a contaminated water well to visualize methane exsolvation in situ.

shale participants informed us that he and neighbors had leased portions of their ranches for multiple oil wells, but that drilling had not yet started to a significant degree in the nearby area. One criticism leveled at our earlier studies was that there were no adequate UD-specific baseline groundwater measurements for quaternary amines, zirconium salts, and biocides used in proprietary fracking mixtures. This West Texas area was an amazing opportunity to sample before, during, and after UD. When we started the study in December 2012, only one oil well had been developed; by January 2014, there were a total of 12 oil wells within 5 km of the 42 water wells we sampled. We observed a drastic pH increase across the majority of the wells, various VOCs, and increased bromide concentrations (6).

## *Neutral and objective*

The publication of these results caused a considerable stir, with a lot of "spin" from all sides of the debate on fracking. Conservation groups took the results as direct evidence of fracking contaminating groundwater, while one industry-led blog touted the report as evidence that many of these perturbations are short-term. While we are often amazed at how our work is interpreted (and misinterpreted), we believe that there is some truth in the old adage "any press is good press".

We find that responding to these agenda-driven interpretations

is best done in person if possible. Though this is not always practical, we have made an effort to attend and present at many public conservation meetings and industry-focused conferences. I'm sure many scientists would cringe at the thought of discussing such a contentious topic with the public, but it has sometimes led to valuable research and donation leads. For example, a fracking watchdog nun, Sister Elizabeth Riebschlaeger, whom our sampling team met in the Eagle Ford shale region, pointed us to Balmorhea, a desert oasis in far West Texas. After discussions with local residents about planned drilling in what came to be known as the "Alpine High" field, we launched a crowdfunding campaign to raise funds to collect baseline data around these coveted springs. The campaign caught the attention of Apache Corporation, the lease holders for the area, who offered to fund a year's worth of water monitoring and laboratory research related to their drilling operations.

The opportunity for us, as academic chemists with no oilfield experience, to discuss general operations, experimental design, and compounds to target has been phenomenal. These days, we can find out what the bottom hole pressure and temperatures are in the Permian Basin with a quick phone call, rather than a lengthy literature search. Other times we hang up from a call with a notebook full of suggested target compounds, based on the company's understanding of breakdown reactions or cross-reactions with other additives in the mixtures. The open dialog has given us a better understanding of the processes at work, and access to the best locations for sampling. And the company has improved its reputation in the region.

Some see the acceptance of the Apache Corp donation as "selling our souls", but we don't believe that receiving industry funding is incompatible with our neutral and objective stance. Donated funds cannot be tied to contractual deliverables, and we are the sole owners of the data. About a month earlier, we received a donation from Earth Day Texas, a conservation organization. Research conducted through funding by both entities will be peer-reviewed and published.

### *Coming together*

Fracking is not going away anytime soon in the US – the financial return is too high. When oil prices collapsed in late 2014, it was easy to see how important the industry was to the economies of states like Wyoming, Oklahoma, Alaska, and North Dakota. Unemployment increased, equipment was abandoned as it became too expensive to operate, and companies filed for bankruptcy.

But we badly need more research into the environmental and health impacts of unconventional drilling. It remains difficult for researchers to gain permission from operators to access pad sites, details of proprietary mixtures of initial fluids, or samples of flowback or produced water (typically sent for disposal by deep well injection). Lack of funding is another major issue. The UD process is complex and entangled with other industrial activities, so definitively conclusive findings are unlikely – not something that attracts grant-giving organizations. Plus, government funding is likely to be limited by the potential negative effects on the country's economy if fracking proves to have undesirable consequences. Therefore, it's likely that private donations will remain the main funding source for our group. We hope that by working with both environmentalist groups and energy companies, we might act as an information bridge between the two sides.

Recently, we took that ethos a step further and did something almost radical: we held a two-day conference with presentations and panel discussions by academic and government researchers, oil and gas regulating officials, industry employees, and conservationists, all open to the public for free. The Responsible Shale Energy Extraction Symposium and Exposition (7) was part of Earth Day Texas 2017, and coordinated with support from EARTHx (formally Earth Day Texas) and the Cynthia and George Mitchell Foundation, both forward-thinking organizations concerned with sustainability and solutions for environmental problems. The meeting was opened by the US Secretary of Energy Rick Perry and saw presentations on health, climate change, chemical disclosure, water use, monitoring technology, and best management practices by operators (8).

### *Reflections*

The past six years have been quite a ride. I've traversed the shale

## Making it CLEAR

The mission of CLEAR is to examine environmental and human health impacts of industrial processes, and develop better technology to detect and remediate industrial contamination.

The lab specializes in testing and monitoring of groundwater and surface water quality in proximity to unconventional oil and gas extraction sites.

CLEAR team members and collaborators are also developing technologies to enable detection and remediation of harmful contaminants that pose a danger to human health, and cultivate the responsible management of natural resources.

*http://clear.uta.edu*
*@LabsOfCLEAR*

## Strange Samples

Samples collected by members of the public have proved valuable to us on several occasions and have found their way into our scientific presentations (9) and manuscripts. Some of the more unusual samples we've been offered over the years have included:

- Vacuum cleaner waste
- Orange water
- Flammable water
- Hair samples taken from the hairbrush of a deceased relative
- Gray fluid that spurted from the ground like a fountain
- Filters from air conditioning units from across an entire neighborhood
- Tail hair from a thoroughbred racehorse
- Fish (bass) caught in the landowner's pond

plays of the USA, visited Hugh Heffner-style swimming pools built with fracking royalties, met conservationist nuns and members of the Professional Rodeo Hall of Fame, and collected samples ranging from the tail hair of a deceased racehorse to mysterious gray bubbling fluid in a coffee can.

Though some of the situations we find ourselves in are funny in the re-telling, we are sensitive to the fact that the homeowners we work with are often in genuine despair. Consumed by the damage they feel is being done to themselves, their families and their land, it's difficult for them to accept that they may never get a clear answer. It's hard to communicate to unsuspecting owners that levels of metals or chemicals in their well water are above those set by the EPA for safe drinking water. But it can be even harder to tell sick homeowners that even though we did all of our fancy tests, we can't tell them why they can't breathe.

For those who are being affected by the impact of UD, our remediation arm aims to help, but developing strategies and products takes far more time than generating data. We are also an academic institution, which ultimately means that our students need to be conducting original, innovative research. We have begun working with various technology firms assessing the effectiveness of their water treatment processes. Recent projects have included a new method for BTEX analysis in soil and characterization of the ability of a commercial household filter to remove organic and inorganic constituents of drilling-produced water. Progress can feel slow, but we hope to eventually be able to work with energy companies, local residents and environmentalists alike to monitor, mitigate and ultimately prevent adverse effects.

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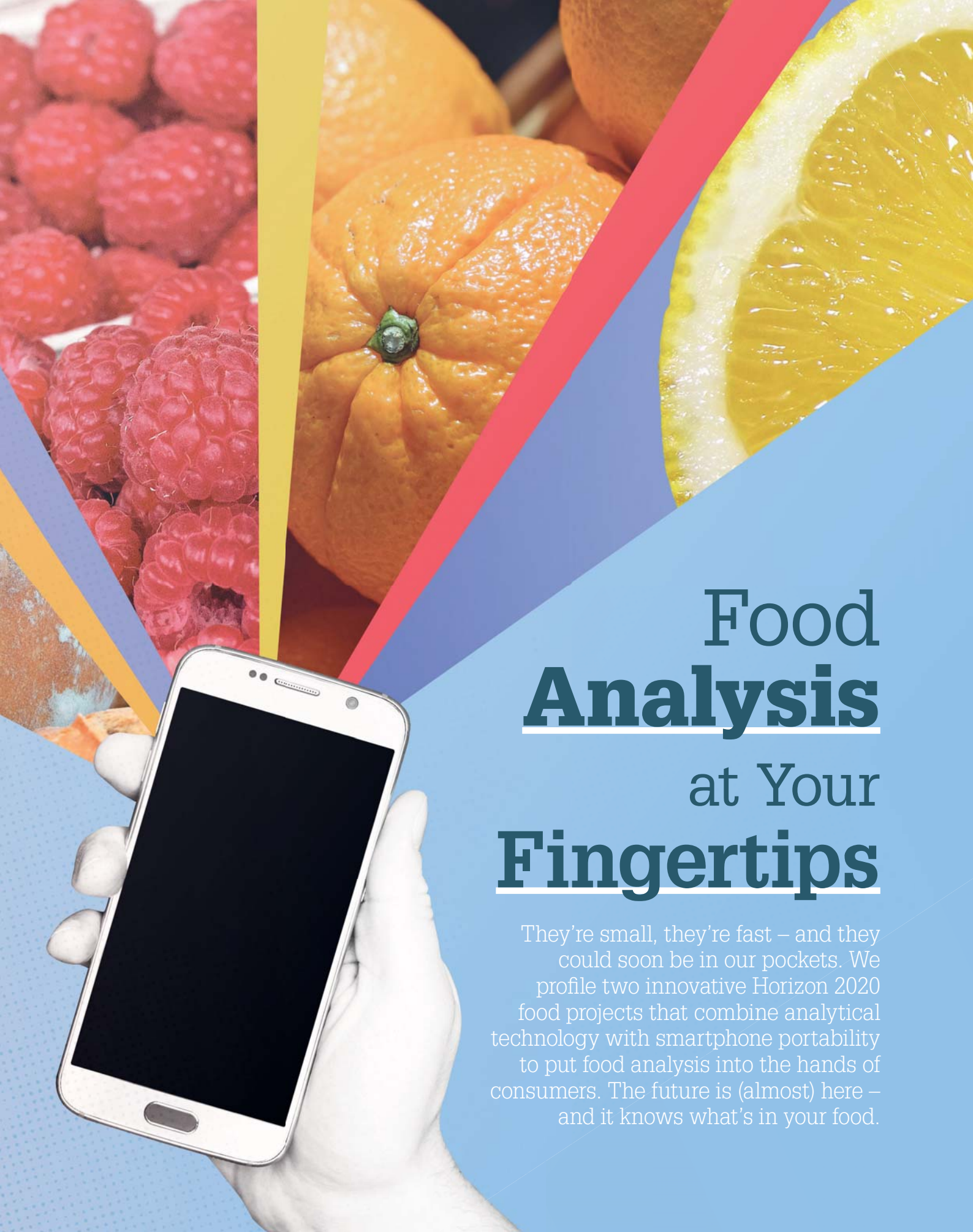

# Food **Analysis** at Your **Fingertips**

They're small, they're fast – and they could soon be in our pockets. We profile two innovative Horizon 2020 food projects that combine analytical technology with smartphone portability to put food analysis into the hands of consumers. The future is (almost) here – and it knows what's in your food.

# SHOOT FIRST, ASK QUESTIONS LATER

Food researchers are joining forces with hardware and ICT developers and mobile phone app writers to build a new type of scanner. Integrating three sensor devices with advanced software, the PhasmaFOOD will provide miniaturized and on-the-spot analysis for the detection of food spoilage and food fraud.

*With Yannick Weesepoel, Researcher Food Authenticity – Food Scanners, RIKILT, Wageningen University & Research*

The whole idea of PhasmaFOOD is to combine different light sensors into an integrated scanner system and build a consumer app around it to make a new generation of light food scanner. So-called heterogenous photonics is the ultimate hardware goal, which basically means that all the elements of a photonic system are fabricated on a single chip to meet size and cost requirements. The device will host three sensor types: two spectrometers and one micro-camera. In addition, three light sources will be integrated with the device to support its sensing functionality. A dedicated PhasmaFOOD mobile app will allow end-users to interact with the device, and the captured data will be communicated via wireless mobile networking to the PhasmaFOOD backend. Analysis results will immediately be sent to users, who will be able to access them at any time and from any location.

Why has portable food analysis suddenly become such a big thing? I think in one way it's very much technology driven; until now, it was not possible to make a chip with an infrared sensor small or cheap enough. It was also not possible for smartphones to operate in such a way. The people making smartphone technology five or six years ago already recognized that people would be using their phones to a much greater extent in the future. Me? I can't remember how good my phone was five years ago – actually, I don't even remember if I had a smartphone! But the interest in food analysis is also consumer-driven; people are suddenly more interested in "scanning" their food – the idea of doing your own analysis, in a simple way, triggers something in people.

## A NEED FOR SOMETHING NEW

When I started here at RIKILT, there were many research position vacancies available. I'd already worked with mass spectrometry during my PhD and wanted to try something new. I'd heard a little about scanners, and thought, "Why not go in that direction?" The fact that the technology would be used by people at home rather than stay in the lab very much appealed to me. Most of the time, during my PhD, this was not the case; you did fundamental, very technical research, which I didn't always find very satisfying. I really like to make things which will be used in real life.

So when I started working here about three years ago, I did some preliminary work on chicken meat. Using a very simple infrared scanner, we attempted to find the water and protein content of the chicken, with the aim of finding out more about how (and how long) it had been stored. The consortium of PhasmaFOOD (George Koutalieris, from INTRASOFT International and Paraskevas Bourgos, from WINGS ICT) began looking for expertise on testing the PhasmaFOOD scanner – and that's how I got involved.

I started acquiring advanced miniaturized IR sensors from Viavi Solutions (formerly JDSU). We began partnering with more companies, and the publicity on food scanners started to build. People started to understand the objective: to revolutionize the use of infrared. It was the beginning of a movement from the lab (a controlled environment) to something completely uncontrolled; from very exact databases to big databases built into an app by non-specialists. Of course, infrared sensors are already being built into phones, but there are still many things you can't do, such as measuring allergens, gluten, lactose or toxins.

Current food scanners – Spectral Engines (the winner of the European Commission's Horizon 2020 food scanner award), SciO (ConsumerPhysics), or TellSpec (the runners up) – are all based on near infrared (NIR) technology. However, NIR spectroscopy is actually somewhat limited in this application; you can scan the macrocomposition of products and even find components that are minimally present (0.1–1 percent). But NIRS struggles to measure very low concentrations of compounds or food spoilage, so more advanced applications are out of reach. We need more information, and that's why we need a new food scanner.

## PERFECT SENSE

Our device works much like any vibrational spectroscopic sensor and must be "trained". For example, if you want to know the moisture content of a piece of meat, the sensor must be presented with different reference samples with different concentrations of moisture within an acceptable range to build a spectral database and a multivariate statistics-based algorithm. If the sensor can actually measure moisture content in a new sample, your model works correctly. If not, you must expand the database to cover more variation in the food samples you present to the sensor. Variation is always a problem with food analysis; to build a functional database, you have to cover a significant amount of natural variation within a given food product. Unlike the pharmaceutical industry, which tends to have narrow concentration windows for all chemicals present, potential variation in food sometimes feels infinite.What is the impact of a different country of origin, a different farm – or even a different cow?

## FOOD FOR THOUGHT

*Michel Nielen is co-chair of the RAFA 2017 food analysis conference in Prague. Here, he tells us what's on the menu this year.*

*Can you give us a roundup of RAFA 2017?*

RAFA is the leading biannual conference on recent advances in food analysis. In November we expect 800+ participants in beautiful Prague. We usually have a large audience and speaker lineup comprised of people who are active in food contaminants (pesticides, antibiotics, POPs), natural toxins and fraud, but we will also cover growing trends in the world of (advanced) food analysis. Food fraud in particular is an ever increasing issue; a couple of years ago, we had only one session about food fraud, but now it is one of the cornerstones of RAFA.

*What's new this year?*

Human biomonitoring is one very interesting new topic that will be covered in RAFA 2017. In current duplicate diet studies, half of the food is consumed, the other half sent to labs for food analysis, so they can measure contaminants or other compounds that have been ingested. You might also collect samples like blood or urine to find a link between analysis of the product and the consumer/consumption. Nowadays, people are searching for alternative means of finding consumption data with contaminants or nutrition value patterns. There is an emerging trend to use head hair specimens, which is borrowed from the forensic field, where hair has been used for drug testing. Your head hair, which grows 1cm a month, represents a chemical archive – the chemical composition of 1cm of your hair correlates with your food (and drug) intake from the last month. It's an entirely new concept for the food analysis field. In fact, it's relatively novel to see people trying to retrieve food consumption and contaminant exposure data from urine and blood. And so, for the first time, we decided to organize a session called "Human biomonitoring related to food" – and we have arranged some high profile speakers.

In food analysis, the focus is traditionally on foods, food products and intermediate products or raw materials. Such samples are being analyzed in labs in line with legislation; for example, maximum residue limits. But we also need to know more about food intake and consumption patterns, to understand the risk of exposure to food-related hazards.

*Are you running a session on portable food sensors?*

Yes, the PhasmaFOOD/FoodSmartphone guys will take the lead in organizing an oral session about smart sensing. There'll also be hands-on demos in a dedicated "smart lab", where people can start playing with food scanners and smartphones and do some testing themselves.

*What are you particularly looking forward to?*

I'm looking forward to the food fraud sessions, as there is a lot of interesting research going on. I'm also very interested in natural toxins; mycotoxins have been studied for many years, but there will be focus on plant toxins, marine toxins and bacterial toxins as well. From the more practical side, multiple pesticide analysis is always a highlight. At RAFA 2015, vendors had instruments in production doing multiple analysis of hundreds or even thousands of food contaminants, in a single analytical run; it's always exciting to look forward to major improvements in mass spectrometry technology both from researchers and instrument vendors.

The project started at the beginning of 2017 with the refinement of the hardware, so the sensors and illumination sources are already available. Design of the prototype – how the electronics, hardware and casing will fit together – is already underway. Designs for the cloud database and the apps have begun, and the team has also performed business case and user case analysis. The main and current analytical task is making reference measurements and using that data to build spectral databases. We are (slowly) testing the sensors for the proposed applications, namely the detection of:

i. mycotoxins and aflatoxins in nuts and grains;
ii. food spoilage and shelf-life prediction;
iii. food fraud and adulteration.

We decided to focus on these three areas because they are particularly tough nuts to crack for food scanners (no pun intended) – and also because of the potential societal impact. Mycotoxins and aflatoxins are very much of interest to the general public because of their potency, but current NIR food scanners fail to reach the typically low concentrations. Spoilage is relevant for people at home, so that they can estimate the age or expiration date of their product (again, very hard for infrared scanners), which could help to reduce food waste. Food fraud – finding melamine in milk or analyzing mixtures of different meat – are also out of reach for NIRS-based scanners.

We are also looking at alcoholic beverages because it's so topical, especially in countries where there are problems with fake drinks or those that contain toxic compounds.

## RECIPE FOR SUCCESS

Multiple partners have come together for the PhasmaFOOD project. We have the leading European IT Solutions and Services Group (INTRASOFT International), an ICT company (WINGS ICT), and cognitive networking lab VizLore, which builds apps and interactive data management systems. Then we have the hardware people from Fraunhofer IPMS, The National Research Council of Italy (CNR), the University of Rome and the Free University of Berlin, who are involved in data compression and communication between different systems. Finally, the Agricultural University of Athens and RIKILT Wageningen

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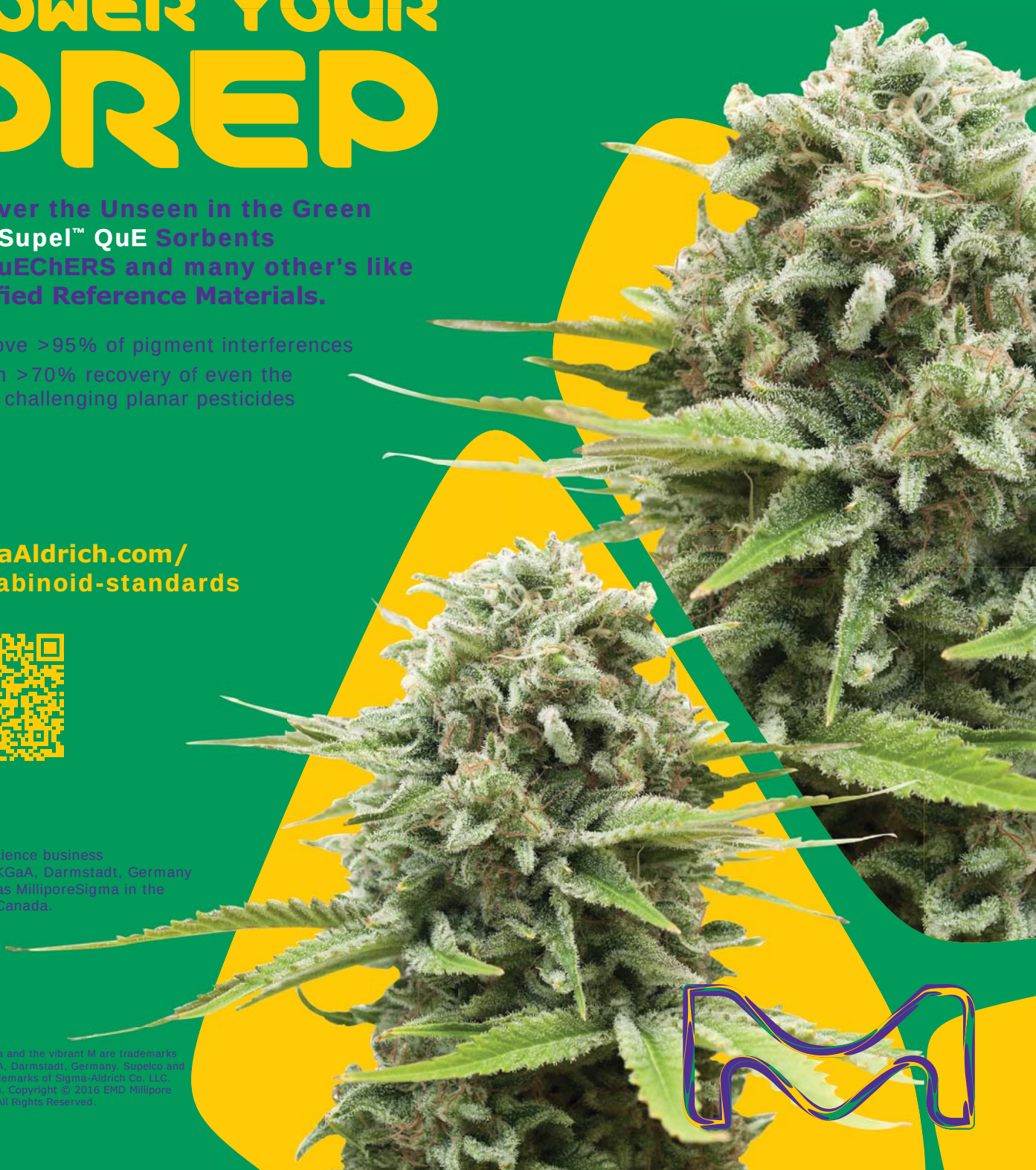
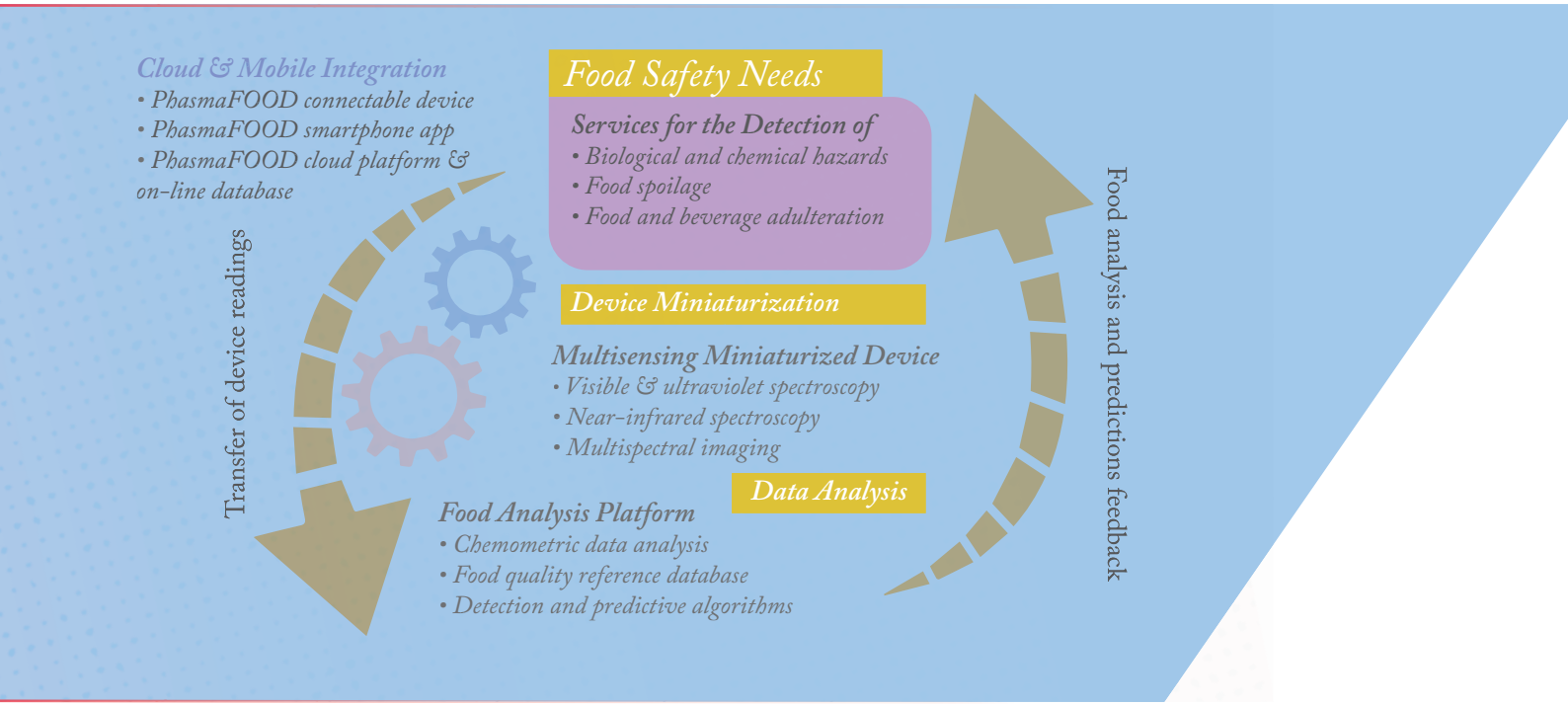


The life science business of Merck KGaA, Darmstadt, Germany operates as MilliporeSigma in the U.S. and Canada.

University and Research are testing the sensors. Wageningen is quite well known for food research, so it's quite a logical choice!

Clearly, the consortium comprises academic and industry partners – and that is, in fact, a requirement for such EU-funded projects; if you submit a purely academic proposal, you would never get a grant. Indeed, there is close to zero fundamental research – everything is aimed at "getting it out there." We have to be at a certain technological level at the end of the project. And though the high-level view of PhasmaFOOD appears pretty straightforward – decide on objectives, make a design, build a prototype, and test it – from a project management point of view, it is highly complex, with many teams working simultaneously on different aspects. For example, we have to make measurements with sensors that are not yet mounted into a prototype, so that as soon as they are mounted, the database will be partly ready.

In PhasmaFOOD, we are going for immediate impact by making the different sensors quite defined. We want give someone who is completely untrained the capability to take a scanner anywhere, and just "point and shoot" – it's a completely new way of using a very old technique.



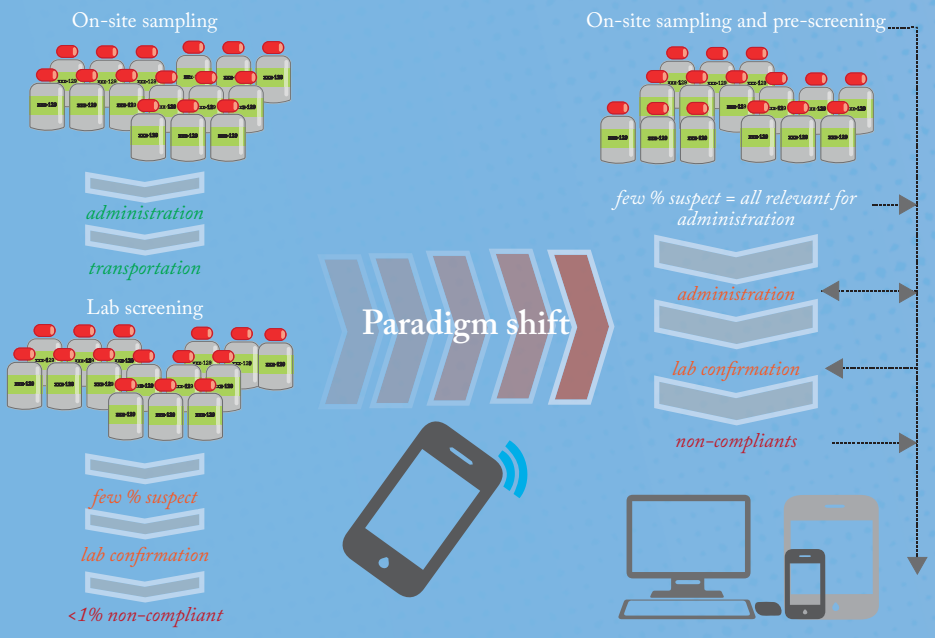

## LET BATTLE COMMENCE

Ensuring food quality and safety can often be an uphill struggle. Could FoodSmartphone – a handheld bioanalytical sensing and diagnostics tool – be a more effective weapon in the fight against food fraud?

*With Michel Nielen, Principal Scientist of RIKILT, professor of Analytical Chemistry at Wageningen University & Research and coordinator of the H2020 MSCA ITN project FoodSmartphone*

In the field of analytical science and technology, a two-sided trend is becoming apparent. In the future, there will be an increase in on-site testing at the point of care in hospitals and GP offices, but also in the field, at farms, in retail spaces – and even at home. And that means a great deal of lab work will move to the end user. At the same time, there is also a trend towards very high-end instrumentation and orthogonal techniques that can measure both biological and physical chemical parameters in a method.

I saw the same trend in food analysis – and that's why two years ago, I applied for a European PhD training network project called FoodSmartphone, which ultimately aims to bring the tools of the routine food analysis lab to end users. I see three different and highly complementary ways of achieving that goal – but all three have different starting points and development times.




## TESTING, TESTING... 1, 2, 3

The first approach is handheld food scanners, which are mainly vibrational spectroscopy- and hyperspectral imaging-driven. Such options rely on what I would call relatively low resolution spectroscopic techniques which, thanks to chemometrics, can offer significant value – particularly for onsite measurement of high-concentration food ingredients, such as moisture, fats, proteins and carbohydrates. "Nutritional value" data is also highly relevant for food traceability and food authenticity. Both the technology and the mathematics are already there. And so, what we can expect in the near future is most likely an integration of different platforms, such as hyperspectral data, combined with NIR and Raman spectroscopy data. You can do quite a lot with these technologies, but you cannot measure residues or contaminants at low levels – and that will never be within reach.

The second approach – where FoodSmartphone sits – addresses how we can drive onsite technology sensitivity down towards maximum residue limits, which means measurements at the sub-ppm level, rather than the percent level. In other words, concentration levels that are relevant to legislation, which also necessitates increased specificity and resolution. FoodSmartphone, at its core, is based on specific bio-recognition – using antibodies and other bioinspired receptors. In essence, we are bringing strip test diagnostic analysis or multiplex immunoassay equipment from the lab to the smartphone platform, and developing solutions for the food analysis field. In reality, this requires a great deal of research in areas such as surface chemistry, biorecognition, microfluidics and image data handling, so we are somewhat behind the starting point of the food scanner approach.

The third approach is also behind, but nevertheless imminent: portable mass spectrometry. In food analysis, mass spectrometry is a key technology – and the field was actually one of the early adopters. Companies are already bringing "compact" MS systems to the market, and at major conferences, you see that several venders and startup companies with the same objective. "Compact" currently means 30–40 kg, with simplified pumping systems, so the sensitivity is not world record-breaking, but may be good enough for at least a part of relevant food applications. You bring them to the field, switch them on and, within 5 or 10 minutes, they are self-tuning and calibrating. However, most of them still require a power and/or gas, so they are not "portable" yet, but rather "transportable". The next phase is to make them truly portable – and that requires much technology development. For example, the mass range and resolution of the 908 Devices instrument is currently not good enough for food analysis requirements, but the user-friendliness of the concept is indeed a good benchmark for future developments.

## BUILDING FOR SPEED

I devised the four-year FoodSmartphone project, and my partners and I applied for and obtained a 2.8 million euro Horizon 2020 grant in 2017. I am the coordinator of the entire program, which equates to about 40 percent of my time! The project has 11 dedicated PhD students working across 11 different strands, which range from biorecognition (and the development of new ligand-binding materials) to the development of smartphone-compatible detection schemes, (3D-printed) microfluidic-based sample preparation, and

image data handling routines. The user interface is important, and throughout the course of the project we will identify best practices and the most promising areas. We will then apply them to specific issues, ranging from pesticides and veterinary drugs to allergens and food spoilage organisms – the real applications of interest.

The scientific challenges are multiple; first of all, the conventional immunoassay approach in the lab is far too slow. Smartphone users want an answer in seconds or minutes, and will not want to wait hours for sample preparation and incubation – so we really must find ways to speed up the process. We also need to make sure these (faster) sample preparation protocols require no training. You cannot expect people to carry out precision pipetting, or precision mixing of reagents – it must be built into a test kit.

Some aspects of the project are beyond my personal knowledge base, so selecting the best partners was critical. I selected each FoodSmartphone partner either for their track record in food analysis or for specific technological skills. For example, at Queen's University, one of the PhD students is very keen on both mathematics and image data analysis, and there is another department focused on nanoscience and nanotechnologies.

Our colleagues in Sweden are doing amazing things with 3D-printed microfluidics – and have a good track record in the engineering of printed optical parts and interfacing them with smartphones. At the end of the project, they will bring us a low-cost 3D-printed device that is capable of precise mixing and pipetting - steps normally done by a technician in a lab - at the press of a fingertip. Now that's simplified sample preparation! Of course, in food analysis, samples and extracts are dirty, so we need filtration devices. Classical filtration is time consuming, so we need well-defined and rapid filtration steps courtesy of the nanoengineering–microfiltration group at the SME Aquamarijn.

By the end of the four years, we hope to have a range of prototypes with a range of demonstrated applicability, along with commercialization plans and future areas for development for the project scientists, who will be postdocs by then. We also want to source companies who can take the project further.

*"Smartphone users want an answer in seconds or minutes, and will not want to wait hours for sample preparation."*

## SOCIAL SHARING

We must not only do good scientific work, but also train our group of PhD students with the future of food analysis in mind and make sure they obtain essential transferable skills. Each student has a personal development plan, which is partly scientific and partly focused on communication skills; for example, presenting to end users or starting their own businesses in (smartphone-based) food analysis. As well as developing proof-of-concept prototypes by the end of the project, we will have nurtured a group of people who can be the frontrunners in the development of the field. I'm very excited about the approach.

When you are designing and developing devices, it's important to communicate with the outside world – and good communication is only going to become more important in the future. For that reason, we decided that one PhD student is "on duty" each week, providing content for the FoodSmartphone blog; talking about adapting to the new environment, and what they are working on throughout the course of the project. Everybody will be able to see what researchers do and face on a daily basis.

We are also very active on Twitter, which is a first for our research. Of the many ongoing analytical science projects, so few use social media, which is a shame; after all, it can make you and your project more accessible and it also raises your profile. Ultimately, we would like to see more close communication, not only with end users from research or QC labs (who are used to finding their way through science journals), but also with a broader range of people – those who I would call non-expert lab operators and technicians. We need to get them involved. It's a major challenge, and a good first step is to be active on social media.

Excitingly, FoodSmartphone is unique. There are people working on smartphone-related diagnostic tools, and though they are exciting from an engineering or image data handling point of view, they simply do not fulfil food analysis requirements. With FoodSmartphone, we have a mixture of people with backgrounds in physics, mathematics, diagnostics and food analysis practice. By combining all our skills and knowledge into a single end-user-focused program – I think we'll be able to make a difference.

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# Keep CLAM... and Forget Sample Prep Bottlenecks

## How automated LC-MS is transforming the world of clinical analysis – and beyond.

*With Davide Vecchietti, LCMS & Life Science Specialist at Shimadzu Italia, Milan.*

First, what is CLAM-2000? In short, it is a fully automated sample preparation module for LC-MS that is based on Shimadzu's time-tested blood coagulation technology. But in reality, it is so much more. Why? Because CLAM-2000 essentially automates the entire LC-MS/MS workflow in a way that few in the clinical analysis field expected. And it heralds a big shift in how LC-MS is likely to continue penetrating the clinical space.

I consider myself lucky to have seen the impact of the CLAM-2000 first hand. I joined Shimadzu during its development, and had the opportunity to spend time with the prototype system installed in Paola Brambilla's Clinical Chemistry Laboratory at Desio Hospital in Milan. It was an exciting and rewarding time – I acted as the interface between clinical expectations and development of the solution, and it was great to see both sides of the story so closely.

### Judging potential impact

Even in its prototype phase, it was clear that many of the features (and the subsequent benefits) were very much appreciated by the users of the system. For example, when we launched the software at Desio for the first time, the staff noted how user friendly it was, and said, "It's even easy to imagine how people with no training in chromatography or mass spectrometry would be able to operate CLAM." From Shimadzu's perspective, it was great to be able to optimize minor aspects of the system (for example, sample loading times and reagent consumption) in the real-life environment for which it is designed.

That was back in 2015, and it gave us complete confidence when we commercially launched the CLAM-2000 in 2016 – the same year it featured in The Analytical Science Innovation Awards (TASIAs). The TASIA judges understood our objective, saying, "Sample preparation is the biggest challenge in most analytical methods. Automation is key to addressing this challenge – especially for biological samples [...] The CLAM-2000 completely automates sample preparation for clinical samples; this could help prevent user error in labs where accurate analysis is of the utmost importance"

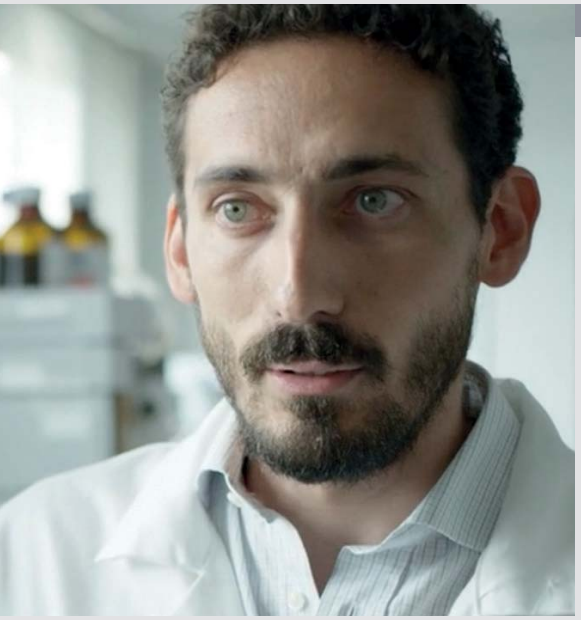
### Automated... but flexible

Despite the "push-button" simplicity and "walk-away" reliability that can come with automated solutions, we understand that we must cater to users of different competency levels – from technicians to clinical laboratory managers. And though the CLAM-2000 LC-MS/MS system works well with commercial kits, many users want the flexibility that comes with a traditional LC-MS/MS system; they want to create new methods or transfer current methods over to the automated system. The need for flexibility comes across very strongly when talking with potential users – and current users, for example, the researchers in the clinical lab at Desio. The CLAM-2000 (unusually) combines simplicity for less experienced users with the complete flexibility or 'openness' that an experienced chromatographer or mass spectrometrist would expect from any other LC-MS/MS system. And that's the real – hopefully not hidden – beauty of CLAM!

### "Curiouser and curiouser!"

Ever since the launch, the clinical community has been very curious about the CLAM-2000 – especially because it was the first fully-integrated LC-MS/MS sample preparation system of its kind. Initial assumptions that it is a "black box" with limited applications are quickly dispelled with the long list of potential analytical applications and the options for further customization and method development, as highlighted above.

But once methods are chosen or developed and approved, the CLAM-2000 system can be operated by technicians who are more familiar with immunoassays, freeing up (sometimes limited) LC-MS/MS expertise for less routine tasks. After all, once the method is locked and loaded, it's a simple case of placing blood collection tubes, reagents, and specialized pretreatment vials into the CLAM-2000, which then performs all processes automatically, right through to reporting of results. Notably, different sample vials can be subjected to different methods within the run. In therapeutic drug monitoring (TDM), for example, you can assign an



analyte to each vial, and the instrument automatically selects the correct sample prep and analytical method.

Not only does it eliminate tedious sample preparation steps (which also frees up technician time) – it also reduces the risk of operator error, increasing reproducibility. In essence, it means you can trust the system to run analyses for hours on end. Moreover, the system has many 'check-points' at the various analytical steps (sample preparation, calibration and so on) so if something does go wrong – a loading error, for example – it's obvious what went wrong and with which sample.

### How are researchers using the CLAM-2000?

Before launch, we were already using the CLAM-2000 for a number of applications at Desio Hospital, including immunosuppressant, steroid and vitamin D determination. These are routine analyses where the superiority of LC-MS/MS is already well known, so they represented a perfect 'proving ground' for an automated clinical LC-MS/MS solution. And we had some pleased and surprised faces when we loaded 20 steroid samples and 20 vitamin D samples, pressed "start," walked away from the instrument and came back to all the results after a couple of hours.

Since then, we've focused more on TDM panels. Here, the CLAM-2000 shows its versatility in terms of matrix – blood, serum, plasma and urine (and even saliva) can all be loaded into the system. And even in the same batch!

### The future of clinical analysis?

I believe fully integrated automation was the final step necessary to make LC-MS/MS accessible to routine clinical laboratories, where sample preparation and such complex analytical techniques are less common. Automation isn't always just about cutting costs or saving time; in this case, it expands the use of a superior technique that offers more accurate and reliable results – and that's a truly exciting and high impact prospect.

*For Research Use Only. Not for Use in Diagnostic Procedures.*

## Clinical Pioneers

**Four researchers share their experiences with CLAM-2000: tas.txp.to/0917/CLAM2000**

"It's possible to walk away from the instrument and allow it to perform hours and hours of work without the intervention of our technicians. I was very impressed with the possibilities the CLAM gave in our laboratory."
*Paolo Brambilla, Clinical Laboratories' Director, Milano-Bicocca University at Desio Hospital, Milan, Italy*

"A main benefit for us is that we can use in-house methods from other LC-MS systems. For one method it's an afternoon's work – so it's very easy to do."
*Lars Kröner, Department Toxicology, Labor Dr. Wisplinghoff, Cologne, Germany.*

"The goal is to implement 24/7 routine analysis of drugs with the CLAM system."
*Frank Streit, Head of Clinical Research, University Medical Center Göttingen, Germany*

"We have compared the old liquid-liquid extraction and solid-phase extraction procedures with the [CLAM-2000] and we gain a lot of time in the preparation of a series of tubes."
*Frank Saint-Marcoux, Department of Pharmacology, Toxicology, and Pharmacovigilance, University Hospital of Limoges, France*

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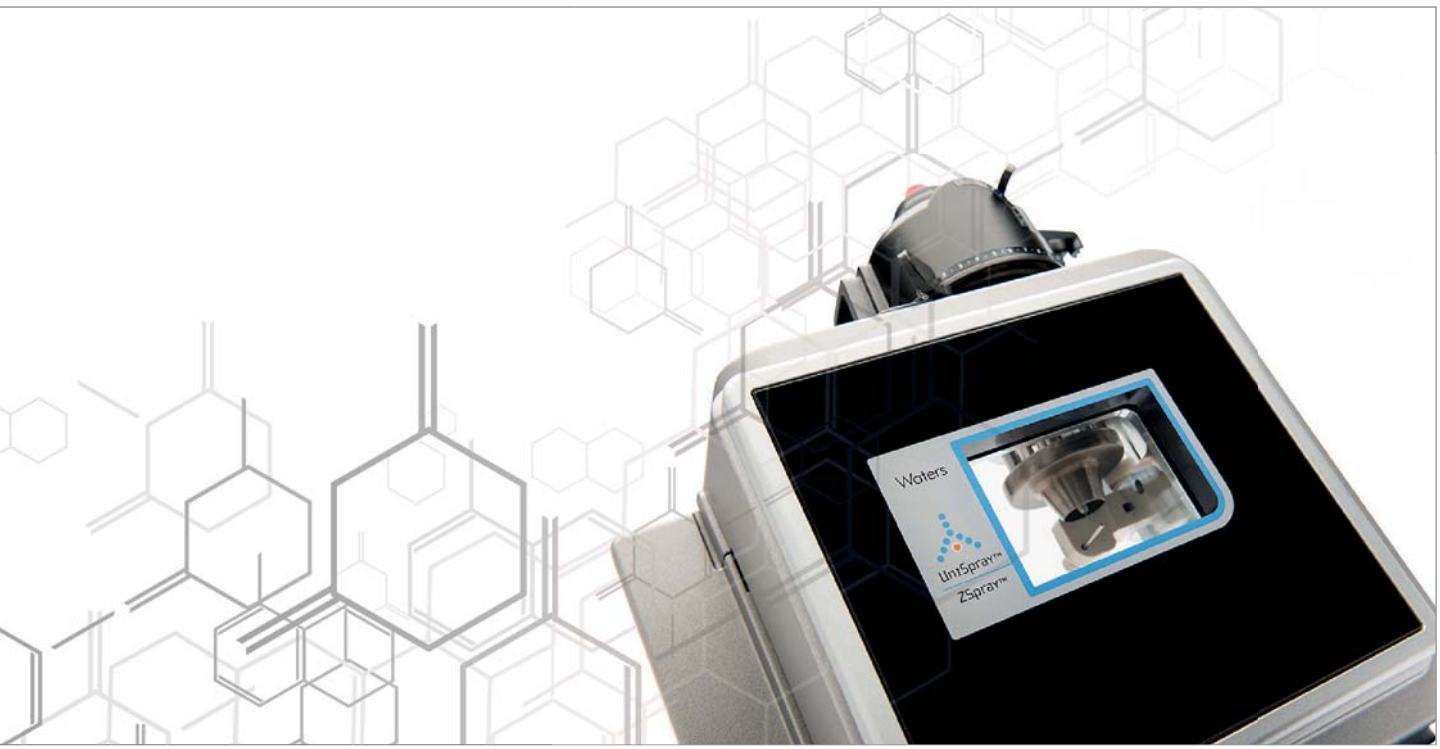
# Perfect Geometry

Does UniSpray's aerodynamic design give it the edge over conventional electrospray ionization?

*By Steve Bajic*




## The problem

Ionization is a critical process in mass spectrometry. All mass spectrometers – no matter how powerful or sophisticated – are highly dependent on the efficient generation of gas phase sample ions in the ion source. Electrospray ionization (ESI) sources have been widely adopted since their commercialization in the late 1980s, and have become the first choice for most day-to-day analyses. However, all ionization mechanisms have limitations; ESI ionization efficiency is compromised at high flow rates and when using highly aqueous mobile phases. To analyze the broadest range of different molecules, analysts must select the most appropriate source and potentially switch sources during analyses.

## Background

Early commercial ESI sources allowed mass spectrometry (MS) to be applied to biological compounds, such as peptides and proteins, which would typically be infused into the source at low flow rates of 1–5 µL/min. Under these low flow conditions, atomization was achieved via a classical Taylor cone (formed at the end of the liquid

capillary), following the application of a few kilovolts between the capillary and the ion inlet cone. More recently, infusion-based analysis for biological applications has been superseded by nanospray ESI capillaries that operate at extremely low flow rates (10–1000 nL/min) and offer high ionization efficiency for small sample volumes.

From a commercial viewpoint, the greatest leap in ESI sources came from the marriage of mass spectrometry and liquid chromatography (LC-MS), which gave analytical chemists access to the enhanced specificity offered by both techniques. To adapt ESI sources to the high flow rates (0.1–1.0 mL/min) typically used in LC (or its modern equivalent UPLC), the atomization process was boosted by the addition of a concentric flow of high-velocity nitrogen gas at the ESI tip. However, when conducting infusion experiments with a fixed analyte concentration from flow rates of 10 nL/min to 1 mL/min, it is common to see the analyte signal increase by a factor of 20 at the highest flow rates, while analyte consumption jumps by a factor of 100,000. The cause? The poor ionization efficiency of high flow rate ESI, which is critically dependent on droplet factors, such as size distribution, charge per unit volume and evaporation rates, as well as additional factors, including inlet sampling efficiency. Ionization efficiency can become particularly challenging when using highly aqueous mobile phases.

## The solution

There is a body of historical evidence to suggest that surfaces play an important role in both the sensitivity and stability of atmospheric pressure ionization

*"From a commercial viewpoint, the greatest leap in ESI sources came from the marriage of mass spectrometry and liquid chromatography."*

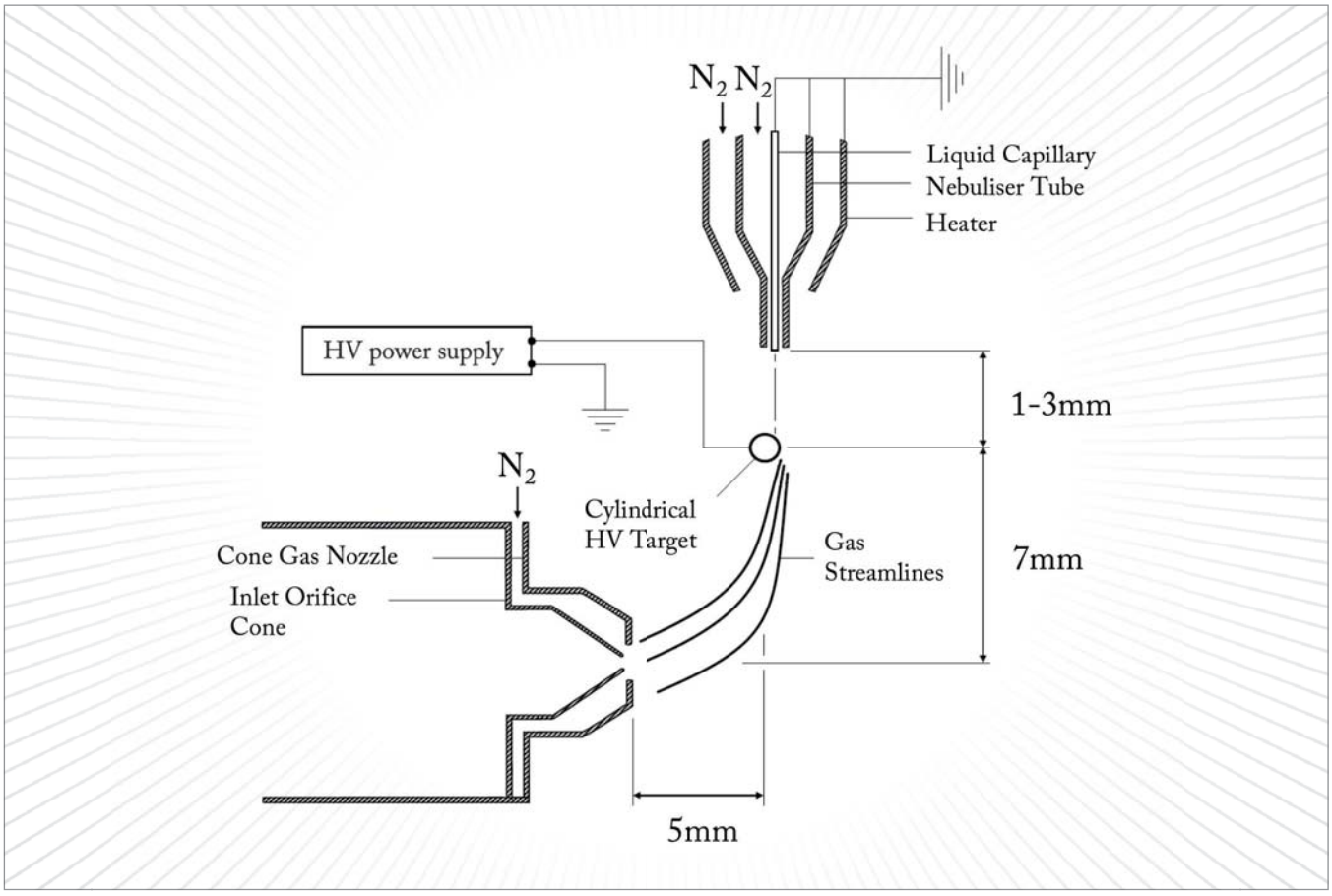



Figure 1. A schematic of the UniSpray API source

sources such as ESI. Although the reasons were not understood, we knew that high velocity sprays that impinge on curved surfaces, in particular, could improve source performance. The ion source described in this article originated from experiments that were designed to optimize these effects and the associated requirement for efficient coupling with the ion inlet of the mass spectrometer.

Work started in early 2011 at Waters' MS Research Centre. In these early experiments, an insulated, tapered high voltage rod target was manipulated three-dimensionally via a microadjuster in the space between the sprayer and the ion inlet cone. The use of a tapered target allowed us to rapidly and accurately determine the effect of target diameter on ion signal. It very rapidly became apparent that significant enhancements in ion signal could be achieved compared to conventional high flow rate ESI by carefully optimizing the geometrical parameters of the experimental arrangement. As a result of this, we found that we were able to increase ionization efficiency by combining a high-velocity spray with a high-voltage, cylindrical target that is positioned in an off-axis, cross-flow arrangement, immediately upstream of the ion sampling cone – we called this novel ionization technique UniSpray™.

*"It very rapidly became apparent that significant enhancements in ion signal could be achieved."*

UniSpray shares some features with high flow rate ESI sources, in that the liquid flow is nebulized by a high-velocity, concentric nitrogen gas flow. However, unlike ESI, the high voltage

is applied to a cylindrical target electrode that is positioned close to the grounded nebulizer, such that the near-supersonic jet impinges on the target surface. A schematic of the UniSpray source is shown in Figure 1. The source is formed by directing a high-velocity, nebulized jet from a grounded sprayer onto a cylindrical metal target that is held at a high voltage and is located between the sprayer and the ion inlet orifice of the mass spectrometer. Nitrogen gas is delivered to the nebulizer tube at a gauge pressure of 7 bar. Under these conditions, the nitrogen jet will be near-supersonic at a distance of a few millimeters from the nebulizer tip.

To optimize source sensitivity, it is critical that the collimated spray impacts on exactly the right point on the cylindrical target. As shown in Figure 1, the maximum signal intensity is typically obtained when the spray is asymmetrically positioned to hit the upper right quadrant of the target. Under these conditions, the gas flow becomes attached to a portion of the curved surface and results in asymmetric gas streamlines in the wake, which are directed towards the ion inlet orifice. This flow phenomenon is known as the Coanda effect. Under the influence of the Coanda flow field, ions and charged droplets are directed towards the ion inlet, which is surrounded by a cone gas nozzle that supports a drying gas flow of nitrogen at 150 L/hr.

UniSpray sources generally enhance ionization efficiency when compared to high flow rate ESI, which can in turn enhance analytical sensitivity. Some general characteristics of the UniSpray source have been studied by Lubin et al., who compared the signal intensity obtained by ESI and UniSpray for small pharmaceutical compounds (16 analytes in positive ion mode and 7 in negative ion mode) with acidic, basic and neutral mobile-phase types (1). Figure 2 shows the signal gains (UniSpray ion intensity divided by ESI ion intensity) obtained at various mobile-phase compositions and for three different flow rates. Here, each point is an average of the pooled data for each compound and each mobile-phase type. From these plots it can be concluded that the signal intensity observed with the UniSpray source is higher on average than the ESI signal for all mobile-phase compositions, with the greatest gains seen under highly aqueous conditions. UniSpray gains in excess of ×20 were observed under certain conditions, but

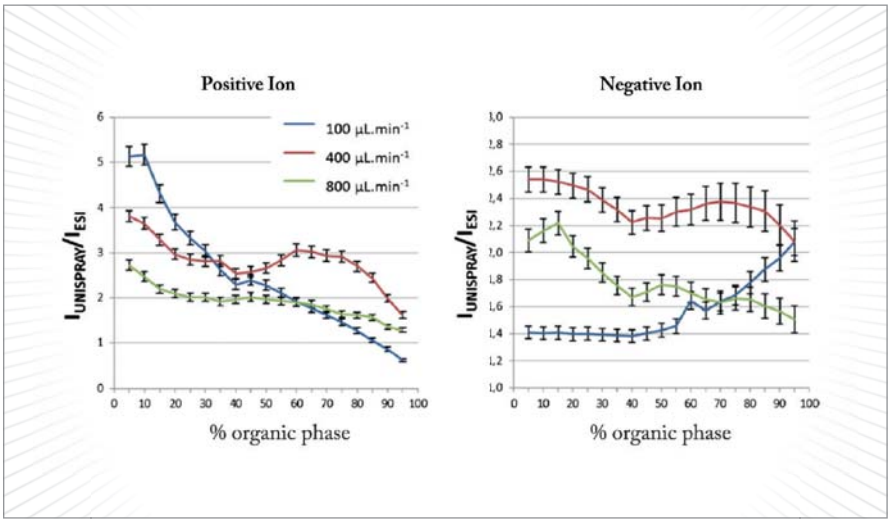



Figure 2 – A comparison of the average signal intensity ratios for UniSpray and ESI versus mobile phase composition for 16 positive ion analytes and 7 negative ion analytes (from reference [1]).

*"UniSpray could allow the consolidation of multiple methods into a single analysis, optimizing laboratory efficiency."*

gains were highly compound-specific, with a few analytes giving greater responses with an ESI source.

The unique geometry of the UniSpray ion source generates several different mechanisms to produce smaller droplets and enhance desolvation. You can read more about these underlying mechanisms at www.waters.com/unispraymechanisms.

## Beyond the solution

UniSpray has the potential to increase the number and type of compounds that can be detected by mass spectrometry in a single run and simultaneously enhance sensitivity. Therefore, UniSpray could allow the consolidation of multiple methods into a single analysis, optimizing laboratory efficiency, and allowing users to see a more complete picture of their samples. Work is ongoing to characterize the behavior of the UniSpray source over a wide range of analyte types, mobile phases and additives for both UPLC and UPC2 applications. I also believe that, as the technology becomes widespread, UniSpray will expand into diverse areas, such as biomolecules, oilfield samples and the ambient ionization of challenging analytes.

*Steve Bajic is a Senior Research Scientist at Waters Corporation, Wilmslow, UK.*

*Reference*

1. *Lubin et al., "Atmospheric pressure ionization using a high voltage target compared to electrospray ionization", J Am Soc Mass Spectrom, 28, 286–293 (2017).*

# Tips, Tricks & Tools

*in Pharmaceutical Analysis*

# THE ANALYSIS OF RESIDUAL SOLVENTS IN PHARMACEUTICAL PRODUCTS USING GC-VUV AND STATIC HEADSPACE

## Introducing a new method for faster sample throughput and shorter GC runtimes

Volatile organic compounds are used in pharmaceutical manufacturing during the production of drug substances, pharmaceutical additives, and drug products. Known also as residual solvents, they account for 50-90 percent of mass in typical pharmaceutical operations and represent most of the process toxicity. Testing for the presence of these solvents, therefore, is critical for patient safety.

Testing commonly follows United States Pharmacopeia (USP) Method <467> guidelines, which suggest a gas chromatography (GC) runtime of 60 min. In addition, it is recommended that Class 1 and 2 solvents be identified and quantitated by complementary methods utilizing different stationary phase selectivity when solvents are found to meet or exceed the permitted daily exposure (PDE) concentration limits.

In this unique application, a gas chromatography–vacuum ultraviolet (GC-VUV; VUV Analytics VGA-100) method was developed to significantly reduce the analytical bottleneck involved in the testing of residual solvents. Experiments were undertaken to demonstrate the chromatographic capabilities of GC-VUV when applied to residual solvent analysis using model pharmaceutical matrices such as generic throat spray. Samples were prepared by mixing 2-mL of water with 25-100 mg/mL of pharmaceutical product and spiking Class 2 Solvent Mix A and B (Restek) to meet the desired concentration limits. The total GC runtime was set to eight minutes and used throughout the GC-VUV residual solvent application.

This method for residual solvent analysis was shown to offer a few key advantages over USP Method 467 experimental conditions. First, VUV absorbance spectra provided authoritative solvent identification as well as compound quantitation. Second, chromatographic compression was possible without any loss of data quality. Runtimes of 8 minutes or less – a 5× or greater reduction – were shown to be sufficient for the analysis of Class 1 and 2 residual solvents. Third, different residual solvent classes could be analyzed in a single run. The VUV detector delivered a linear, highly reproducible response at concentrations ranging from 2× to 0.1× the Class 1 and 2 PDE detection, and the ability to deconvolve analyte co-elution.

In summary: the analysis of residual solvents by GC-VUV delivers a single method for the identification and quantitation of toxic compounds in pharmaceutical products.

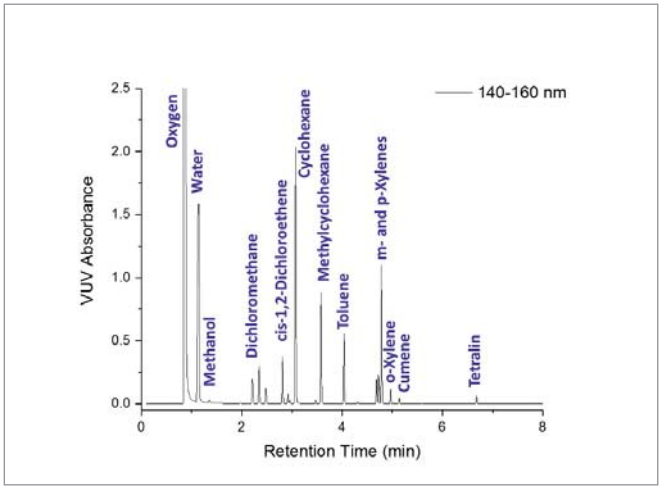



Figure 1. Compressed gas chromatogram showing Class 2 residual solvents separated and identified in less than eight minutes. The typical runtime for the USP 467 method is 60 min.

# HIGH-THROUGHPUT FORMALDEHYDE ANALYSIS IN AIR USING DIRECT MASS SPECTROMETRY

Direct analysis using selected ion flow tube mass spectrometry (SIFT-MS) enables real-time monitoring of formaldehyde to sub-part-per-billion concentrations, and simplifies and accelerates both sampling and analysis, providing 25-fold throughput enhancements.

*By Mark J. Perkins, Anatune Limited and Vaughan S. Langford, Syft Technologies Limited*

The toxicity, carcinogenicity and ubiquity of formaldehyde necessitates detection at trace levels across diverse applications, including pharmaceutical testing, automotive emissions, and ambient and indoor air quality. Formaldehyde is, however, difficult to analyse to trace levels using gas chromatography (GC) and liquid chromatography (LC); GC and LC usually require sampling of large gas volumes to achieve low detection limits, followed by derivatization to enable analysis of this highly polar, reactive compound.

SIFT-MS revolutionizes formaldehyde sampling and analysis by applying very soft chemical ionisation. SIFT-MS eliminates chromatography and directly analyses formaldehyde in air to sub-part-per-billion concentrations (ppbv; by volume) within seconds, from only a few millilitres of air. This yields very high sample throughputs in the laboratory, and enables continuous monitoring – with a time resolution of a few seconds – in process applications.

The formaldehyde data shown here were obtained using a Syft Technologies Voice200ultra SIFT-MS instrument, integrated with a GERSTEL Multipurpose Sampler (MPS; GERSTEL, Mülheim an der Ruhr, Germany). Sampling from Tedlar gas sample bags (SKC, Eighty-Four, PA, USA) was achieved using the GERSTEL sample bag analysis accessory.

SIFT-MS has a linearity range that typically extends six orders of magnitude, with detection limits in the low part-per-trillion (pptv) concentration range. Figure 1 shows linear detection of formaldehyde from very low ppbv to mid-part-per-million (ppmv) concentrations, without requiring any preconcentration or sample dilution. This concentration range covers the needs of most applications in the pharma, automotive and environmental industries.

Formaldehyde analysis using SIFT-MS is highly repeatable. Figure 2 shows four replicate injections of a 200-ppbv formaldehyde gas standard taken from a Tedlar sampling bag. The mean concentration reading was 203 ppbv with an RSD of 2.6 percent.

Direct analysis of formaldehyde in air is straightforward using SIFT-MS – by eliminating chromatography, 25-fold sample-throughput enhancements can be achieved.

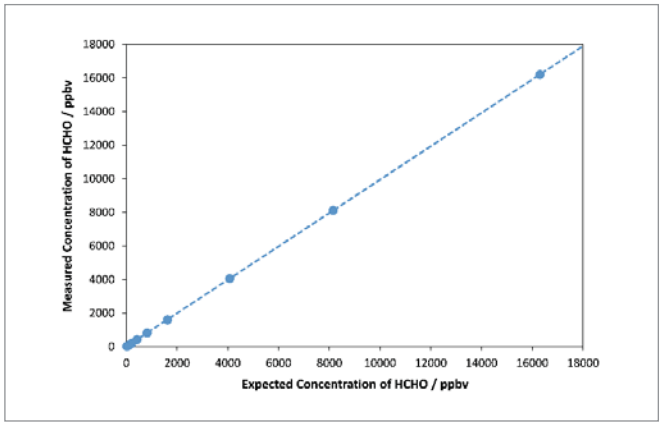



Figure 1. SIFT-MS linearity for formaldehyde analysis across the ppbv to ppmv range.

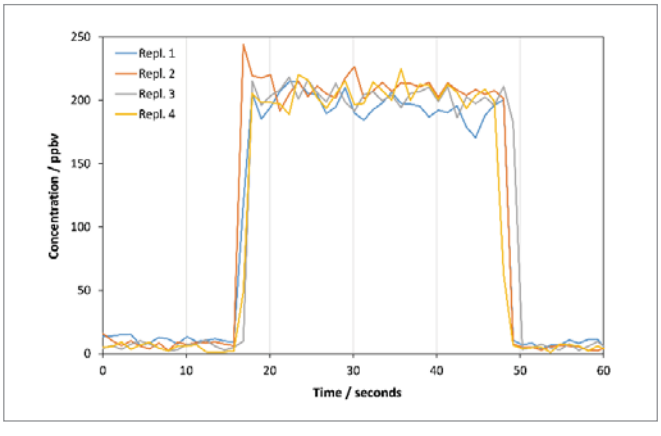



Figure 2. Rapid, replicate analyses of formaldehyde direct from a Tedlar sample bag using automated SIFT-MS.

# Putting Theory Into Practice

**Sitting Down With… Attila Felinger,** Professor of Analytical Chemistry, University of Pécs, Hungary.

### Did you always know you would be a chemist?

My passion for chemistry started very early – I remember reading chemistry books in elementary school. I chose a high school that specialized in chemistry and went on to study chemical engineering at University of Veszprém, Hungary, where I did my Bachelor's and Master's theses in analytical chemistry.

My research has always been driven by curiosity. It's human nature to want to understand how something works – just as a keen driver wants to understand their car, a chromatographer wants to understand their column. In my analytical chemistry research I incorporate elements of chemical engineering and physical chemistry, to understand the theory behind the instruments.

### How has the field evolved?

Ten or fifteen years ago, it was widely held that we had reached the limits of liquid chromatography. Then UHPLC came along and suddenly there was a wealth of new opportunities and problems for us to get to grips with. The advent of core-shell particles brought another raft of novel possibilities, and now we wait with interest to see what changes 3D printing technology might bring in the next few years.

### What is the current focus of your lab?

We explore the fundamental processes of separation science, with the ultimate goal of developing better tools. For example, we investigate how the chromatographic column or bed contributes to loss of efficiency during reverse-phase chromatography and UHPLC. We are also trying to understand the retention mechanisms involved in zwitterionic chiral stationary phases, and supercritical fluid chromatography – all areas where the underlying processes are not well understood.

HPLC is a mature technology, applied in laboratories everywhere. However, the approach to fine-tuning a method is often what you might call "inject and watch" – a time-consuming process of adjusting different parameters until you get the result you want. Once you understand the fundamental physical and chemical processes taking place inside the column, you are equipped to optimize your separations quickly and efficiently.

### What have been the key turning points in your career?

In 1989, when I was still a young postdoc, I had the opportunity to go to Italy to work with Francesco Dondi at the University of Ferrara, which began a longstanding collaboration. Together, we helped demonstrate the many benefits of molecular-level (stochastic) modelling of chromatography. Unfortunately, this approach is still not fully appreciated or frequently used, but I hope in the future it will attract broader interest and acceptance.

A year later, I joined Georges Guiochon's group at the University of Tennessee, where I spent three years that shaped my whole career. I learned so much from him about how to approach chromatography – and life. He would choose an area of separation science that was poorly understood and spare no efforts to systematically reveal its secrets – an approach I have tried to emulate. Georges and I became great friends and continued to collaborate until his death in 2014.

### What's next for your group?

We will continue our work in chiral separations and supercritical fluid chromatography, separately and in combination. As always, we want to answer fundamental questions in chromatographic separations – what controls and limits the separation, and how can we optimize it?

### And for the wider field?

Chromatography is here to stay. I've learnt in the course of my career that chromatography has a wonderful ability to renew itself. It's impossible to say how chromatography will look in 10 or 20 years, but I'm confident it will remain one of the strongest applications in analytical chemistry.

I'm a member of the scientific committee for the HPLC symposium series, which helps me to stay current with trends in the field and the work of young scientists. There was a fascinating lecture at HPLC 2017 in Prague by Zoltán Takáts (Imperial College London) about the iKnife, which is bringing analytical science to the surgical theatre. I think in the future we can expect to see analytical chemistry becoming a part of everyday life.

I am also President of the Hungarian Society for Separation Sciences, which organizes an event every year – alternating international and domestic symposia. Like HPLC, we make it our mission to bring together young and established scientists in an open, collaborative atmosphere.

As a scientist, you cannot concentrate solely on your own career, or even your own field. If you have an opportunity to help the wider community, or support the next generation of scientists, you must take it.

### What is the biggest challenge facing the field?

I find it worrying that analytical science is often seen as being at a lower level than organic, physical, or theoretical chemistry. Some don't even consider analytical chemistry a discipline in its own right, but rather as "applied physical chemistry". I strongly disagree. Recruiters in pharma, healthcare and environment are heavily focused on hiring specialists in instrumental analysis or analytical chemistry, and often struggle to fill these vacancies. To make sure we can meet the needs of society, it's important that analytical chemistry is recognised as an independent discipline with a crucial role.

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