

the Analytical Scientist®

Upfront

Algal doom and Alzheimer's disease inclusion

06

In My View

Sample preparation takes center stage

12

Feature


Citizen science: a new era in analytical chemistry?

26 – 37

Sitting Down With

Food safety fanatic, Michel Nielen

50 – 51



The (Long and Winding) Road to LPGC-MS

Three trailblazers recall the arduous journey to low-pressure GC

16 – 25



Suits perfectly

Grows according to needs

The brand-new AOC-30 series of automatic sample injection systems for gas chromatographs benefits routine analysis work in pharmaceutical, chemical and environmental. Available as Single and Dual Tower solution, the AOC-30 series achieves high throughput with a capacity of up to 150 vials. Equipped with unique technologies and functionalities, the automatic sample injection system is suited perfectly to automation, productivity and remote operability needs of next-generation laboratories.

Precise results and long-term operation

based on features such as intelligent syringe wash and Xtra live septum for extended service life

Grows flexibly with lab's future needs

through customizable accessory set-up options and many upgrade possibilities

Expert-level measurement results

ensured by "Analytical Intelligence" functionality started with just a click

Application-specific configuration

through various syringe sizes allowing flexible injection volumes



www.shimadzu.eu/suits-perfectly



**ANALYTICAL
INTELLIGENCE**

The Analytical Intelligence logo is a trademark of Shimadzu Corporation.



It's not hard to see why science appears somewhat elitist to outsiders. Those among its upper echelons typically hold multiple degrees in challenging subjects from prestigious institutions, often with awards lists as long as your arm. And that's not a criticism, mind you – just an observation. Nevertheless, I can't help but wonder if this status quo underscores much of the disconnect we see between scientists and the public...

One trend that can bridge these two groups? Citizen science. Described as “the democratization of science” by Michel Nielsen in this month's second feature (page 32), it could help bring research access to the masses. Today's public is welcome (and even encouraged) to contribute to studies on all manner of subjects – from monitoring the effect of light pollution on the visibility of constellations in the night sky to a good old-fashioned avian census.

Analytical science, by its very nature, must take the idea one step further; for example, by empowering the citizens with smartphone-linked mini-machines that can assess food safety or detect disease. But who are the winners in this relationship? What we're talking about is a symbiosis; the general public buys into and directly benefits from the hard work of scientists, meanwhile the scientists (hopefully) benefit from previously unobtainable pools of data and renewed (or newfound!) interest in the research subjects they hold so dear.

In the age of anti-maskers and climate change-deniers, perhaps such mutually beneficial interaction could exert effects that reach far beyond what one might first anticipate. After all, we must all work together if we are to tackle the great crises facing humanity. Green chemistry is almost certain to play a pivotal role in our field's own contributions to sustainability – see what Elena Ibañez of the Sample Preparation Study Group and Network has to say about that on page 16.

Innovation will also be needed to guide us to a brighter (or simply tolerable) tomorrow – the need for measurement science can only significantly and continuously increase. Could low-pressure GC give us the speed and simplicity we need to ramp up testing efforts to unprecedented levels? Perhaps – but turn to page 20 to make up your own mind.

I, for one, am excited to see how analytical – and citizen – science evolve in the future. After all, working at *The Analytical Scientist* certainly grants us wonderful insights – but not the power or tools to wield analytical science for personal ends! (Could somebody please let me know when smartphone spectrometers are about to hit the consumer market?)

Matthew Hallam
Editor



08

- 03 **Editorial**
A Democracy for Discovery,
by Matthew Hallam

On The Cover



*Despite the obstacles,
LPGC has persevered.
Here, we chose to portray this
(arduous) journey with a classic
image of endurance.*

Upfront

- 06 Quick reads on the latest
research, from an answer to
the mysterious eagle deaths
plaguing the US, to a cheap and
rapid test for COVID-19



12



20

In My View

- 12 **Giorgia Purcaro** discusses
the importance of sample prep
in multidimensional analysis
- 14 There are a number of key
considerations chemists must
take into account to optimize
sample prep success - **Verónica
Pino** shares why material choice
is one of them
- 16 **Elena Ibáñez** discusses the
importance of green analytical
chemistry in meeting the
Sustainable Development Goals
set out by the UN

Feel free to contact any one of us:
first.lastname@texerepublishing.com

Content Team

Editor - Matthew Hallam
Lauren Robertson (Deputy Editor)
Frank van Geel (Scientific Director)

Commercial Team

Publisher - Lee Noyes
Gaurav Avasthi (Business Development Manager)
Nick Ransom (Business Development Executive Americas)

Design Team

Head of Design - Marc Bird
Hannah Ennis (Senior Designer)
Charlotte Brittain (Designer)

Digital Team

Digital Team Lead - David Roberts
Peter Bartley (Digital Producer Web/Email)
Abygail Bradley (Digital Producer Web/App)

Audience Team

Audience Growth Strategy Manager
- Brice Agamemnon

CRM & Compliance

CRM & Compliance Manager - Tracey Nicholls
Hayley Atiz (CRM Assistant)

Commercial Support Team

Internal Systems Manager - Jody Fryett
Dan Marr (Campaign Reporting Analyst)

Commercial Services

Commercial Service and Social Media Manager - Matt Everett
Kevin O'Donnell (Marketing Executive)
Alice Daniels-Wright (Video Project Manager)
Jess Lines (Project Support Coordinator)
Lindsey Vickers (Sales Support Project Manager)
Jennifer Bradley (Sales Support Coordinator)

Marketing Team

Marketing Manager - Katy Pearson
Jo Baylay (Marketing Executive)

Accounts Team

Kerri Benson (Accounts Assistant)
Emily Scragg (Accounts Apprentice)

Human Resources

Human Resource Manager - Tara Higby

Management Team

Chief Executive Officer - Andy Davies
Chief Operating Officer - Tracey Peers
Senior Vice President (North America) - Fedra Pavlou
Financial Director - Phil Dale
Commercial Director - Richard Hodson
Content Director - Rich Whitworth

Change of address info@theanalyticalscientist.com
Hayley Atiz, The Analytical Scientist, Texere Publishing Limited,
Booths Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK

General enquiries

www.texerepublishing.com | info@theanalyticalscientist.com
+44 (0) 1565 745 200 | sales@texerepublishing.com

Distribution: The Analytical Scientist (ISSN 2051-4077),
is published monthly by Texere Publishing Limited, Booths
Park 1, Chelford Road, Knutsford, Cheshire, WA16 8GS, UK.
Single copy sales \$15 (plus postage, cost available on request
info@theanalyticalscientist.com). Non-qualified annual
subscription cost is available on request.

Reprints & Permissions - tracey.nicholls@texerepublishing.com

The copyright in the materials contained in this publication and the typographical arrangement of this publication belongs to Texere Publishing Limited. No person may copy, modify, transmit, distribute, display, reproduce, publish, license or create works from any part of this material or typographical arrangement, or otherwise use it, for any public or commercial use without the prior written consent of Texere Publishing Limited. The names, publication titles, logos, images and presentation style appearing in this publication which identify Texere Publishing Limited and/or its products and services, including but without limitation Texere and The Analytical Scientist are proprietary marks of Texere Publishing Limited. Nothing contained in this publication shall be deemed to confer on any person any licence or right on the part of Texere Publishing Limited with respect to any such name, title, logo, image or style.

The Analytical Scientist is printed using soy ink



32

Features

- 20 **The (Long and Winding) Road to LPGC-MS**
Three trailblazers on LPGC's journey recount the obstacles that sprung up during development, and share how the technique managed to persevere
- 32 **Empowering the Analytical Scientist in Everyone**
Michel Nielen wants to bring science to the masses. The advantages are clear, but what obstacles do we face?

Departments

- 42 **Solutions: NIST research chemist Melissa Phillips tells us about the aims of their cannabis quality assurance program**

Sitting Down With

- 50 **Michel Nielen, Principal Scientist of Wageningen Food Safety Research (WFSR) and Professor of Analytical Chemistry at Wageningen University, Wageningen, the Netherlands**

Editorial Advisory Board

Chris Harrison, San Diego State University, USA
Christina Jones, Research chemist, NIST, USA
Emily Hilder, University of South Australia, Australia
Frantisek Svec, University of

California at Berkeley, USA
Gary Hieftje, Indiana University, USA (Retired)
Hans-Gerd Janssen, Unilever Research and Development, The Netherlands
Ian Wilson, Imperial College London, UK
Jenny Van Eyk, Director of the Advanced Clinical

Biosystems Research Institute, USA
Luigi Mondello, University of Messina, Italy
Martin Gilar, Waters, USA
Michelle Reid, Cristal Therapeutics, The Netherlands
Monika Dittmann, Independent Analytical Scientist, Germany

Peter Schoenmakers, University of Amsterdam, The Netherlands
Robert Kennedy, University of Michigan, USA
Ron Heeren, Maastricht University, The Netherlands
Samuel Kounaves, Tufts University, USA

Algal Doom

After 25 years, we might finally have an explanation for the mysterious deaths of bald eagles across America

When bald eagles started dropping dead in Arkansas in the mid-90s, scientists were stumped – in part because of the strange ways that these birds acted. Some flew into cliff faces. Others stumbled about drunkenly on the ground. Suspected causes from known toxins to infectious disease were explored, but a definitive answer remained elusive.

Twenty-five years later, we may finally have one...

The first clue? A cause of death: avian vacuolar myelinopathy (AVM). The birds were dying because of lesions in their brains and spinal cords. “We know of more than 130 bald eagles that have died since the discovery of AVM in 1994,” says Timo Niedermeyer, a researcher from Germany’s Martin Luther University who tackled the bizarre events. “When the disease first arose, it killed around 70 percent of the bald eagles wintering at DeGray Lake, and it was later found to affect waterfowl, fish, amphibians, reptiles, and crustaceans, too!”

Therein lies clue number two: proximity to specific bodies of water. Timo says,

“These affected waters had one thing in common: dense aquatic vegetation, especially *Hydrilla*.” But there were areas where *Hydrilla* grew and no AVM occurred, so what factor made the deadly difference in some places? Upon closer inspection, a previously unidentified cyanobacterium was found on the *Hydrilla* in affected lakes. A suspect at long last...

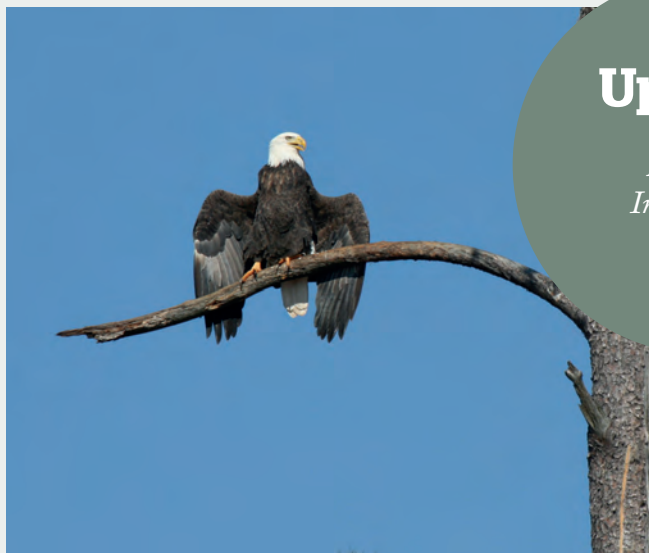
“I received a sample of the cyanobacterium in 2010,” Timo told us. “We purified it, but (extremely) slow growth of the strain meant that it took us 18 months to accumulate enough of it to feed to chickens and test our theory.” After all that time, the cyanobacteria did not cause AVM in the chickens and the project was almost discontinued. But then Timo’s team had another thought: what if the cyanobacteria present in the lakes produced different metabolites to those grown in the lab?

MS imaging was used to analyze the cyanobacterium in its true environment. To the researchers’ delight, a metabolite absent from the laboratory cultures was detected. “The metabolite was spectacular,” Timo explains. “The sum formula was unknown, but it contained five bromine atoms. This explained why the metabolite wasn’t produced in the lab – there was no bromine available there!” Analysis using NMR, infrared, high-resolution MS, and X-ray crystallography then dove a little deeper.

From there, another team was able to show that this novel toxin caused AVM with relative ease! But that’s not the end of this story. “Now we need to find out where this bromide is coming from,” Timo explains. “Higher bromide concentrations are unusual in freshwater and, though it may have natural origins, it’s likely that human activities are to blame.”

Upfront

Research
Innovation
Trends



INFOGRAPHIC

Fare Share

We explore the stats behind food fraud across the globe

WHAT IS FOOD FRAUD?

There are a number of definitions out there, but the European Commission defines food fraud as “any suspected intentional action by businesses or individuals for the purpose of deceiving purchasers and gaining undue advantage.” It encompasses adulteration, tampering, product overrun, theft, diversion, simulation and counterfeiting.

MOST COMMONLY ADULTERATED FOODS

Fish/ seafood
Dairy
Meat
Alcoholic beverages
Oils/fats





BUSINESS IN BRIEF

- Jim Waters, founder and leader of Waters Corporation, sadly passed on May 17, 2021 at 95 years of age. His invaluable contributions to the analytical universe are evident in the feats achieved in labs around the world each and every day (1).
- Thermo Fisher has joined forces with the UK's University of Sheffield to develop end-to-end workflows to characterize and monitor oligonucleotide and mRNA products. The approaches will combine magnetic bead sample preparation technology with high-resolution accurate MS to assess emerging vaccines and drug products (2).
- Peak Scientific have partnered with eForests, a UK-based not-for-profit, with the aim of planting a tree for each gas generator sold as of April 2021. The initiative supports the company's mission to improve sustainability across their operations (3).
- Jeol and Rigaku have launched the XtaLAB Synergy-ED – a new and fully integrated electron diffractometer for the determination of three-



- dimensional molecular structures. The product will likely find a home in drug discovery, synthetic chemistry, and material science (4).
- Shimadzu and Shionogi have signed a basic agreement to work towards a wastewater-based early detection system for the monitoring of infectious diseases, including SARS-CoV-2. Increased sensitivity will be key to the success of these methods in eastern countries like Japan, where cases are much lower than the US and Europe; the partnership will tackle such challenges head on (5).

References

1. <https://bit.ly/3gC9H5e>
2. <https://bit.ly/35y366F>
3. <https://bit.ly/3gwTrDC>
4. <https://bit.ly/3iSq4x5>
5. <https://bit.ly/3q2tajG>



More Secrets of the Mary Rose

Henry VIII's prized flagship had a multi-ethnic crew, according to multi-isotope analysis of teeth

Multi-isotope analysis of remains from the Mary Rose has offered insight into the true diversity of Tudor England (1); specifically, the researchers combined strontium ($^{87}\text{Sr}/^{86}\text{Sr}$), oxygen ($\delta^{18}\text{O}$), sulfur ($\delta^{34}\text{S}$), carbon ($\delta^{13}\text{C}$) and nitrogen ($\delta^{15}\text{N}$) isotope analysis of dental samples to reconstruct childhood diet and origins of eight crew members.

There has been little isotope analysis performed on post-medieval remains in Britain, so it is interesting that the provenance isotope data presented suggests that up to three crew members were from warmer climes than Britain.

Co-author Alexzandra Hildred, said (2): "We never expected the diversity to be so rich. This study transforms our perceived ideas regarding the composition of the nascent English navy."

References

1. J Scorrer et al., *R Soc Open Sci*, 8 (2021). DOI: 10.1098/rsos.202106
2. *The Mary Rose* (2021). Available at : <https://maryrose.org/news/multicultural/>

MOST NOTORIOUS FOOD FRAUD CASES

1981 Olive oil

Industrial rapeseed oil was contaminated with the toxic compound, aniline, and sold as "olive oil" to unwitting street vendors across Spain. This led to more than 1000 deaths.

2007 Pet food

Melamine would make a bigger splash in a year's time, but it first hit the papers after thousands of pets in the US died because they'd been given food tainted with the compound.

2008 Melamine milk

A number of Chinese companies were found to be watering down their milk and adding melamine to bypass protein tests. This led to over 50,000 children being hospitalized.

2009 Peanuts

Seven people died and hundreds fell ill when the Peanut Corporation of America knowingly shipped salmonella-contaminated peanut butter across the US.

2013 Horsemeat

Mostly affecting the UK and Ireland, the "horsemeat scandal" arose when equine DNA was found in frozen beefburgers sold in several supermarkets.

Alzheimer's Disease: Inclusion Matters

Renā Robinson tells us about her ongoing research into the importance of diverse patient groups in Alzheimer's studies

Can you tell me a bit about your recent work in Alzheimer's disease?

Over the last few months we've really been advancing our efforts to use proteomics and lipidomics for testing biospecimens from representative samples of underrepresented groups – mostly African American and Black adults. Our recent work kicked off with a pilot paper we published that looks at postmortem brain tissue from a small cohort of African Americans and non-Hispanic whites. The aim was to determine whether we could see any differences in protein biomarkers when we stratified based on how individuals self-reported their race. This gave us the initial insight that there might be some

significant differences in the proteome between people from different ethnic groups, but it also highlighted that a majority of pathways seem pretty consistent regardless of who presents with Alzheimer's disease.

What are the next steps for your research? We are now equipping ourselves to handle larger numbers of samples from studies with a significant representation of African American, Hispanic and Latinx adults. The core driver behind this is an NIH grant that was funded to enable us to study hypertension as a risk factor for AD and to examine how biochemical markers can be used to evaluate that risk.

What's the biggest takeaway from this research?

The biggest thing we've learned from these studies is that you absolutely have to look at a lot of people across diverse ethnic groups. A lot of what we know about disease has come from a European-centric, non-Hispanic white cohort. Before we can even generalize within the African American community, we need a broader set of individuals to partake in these studies to ensure they are as representative as possible. This doesn't just benefit African Americans; it benefits us all by ensuring we better understand the disease as a whole.

Read the full interview online:
<https://bit.ly/35HEPLw>

Measuring Munch's Crayons

Analysis of the artist's pastel crayons provides a rare glimpse into a favored tool that is often overlooked in technical studies

Unlike their counterparts, pastel crayons appear to have been neglected in technical studies into the composition of modern painting materials. Recently,

researchers tried to rectify this by performing a multi-analytical study of 44 crayons belonging to revered expressionist artist Edvard Munch.

The researchers used a combination of X-ray fluorescence spectrometry, FT-IR, Raman, surface-enhanced Raman spectroscopy, pyrolysis GC-MS, LC-MS and HPLC-HRMS to elucidate the composition of the crayons.

The results showed the crayons were oil-based, with the main binding media being beeswax, palm oil or Japan wax in different relative abundances dependent on

the brand of crayon. Overall, the synthetic and organic pigments used in both brands were largely similar, with the exception of the greens; these were made using either Prussian blue and chrome yellow, or a mix of viridian, ultramarine and lead chromate. The researchers believe the detailed results will aid conservation strategies for both Munch's and other 19th century artists' works.

Reference

1. J La Nasa et al., *Scientific Reports*, 11 (2021).
DOI: 10.1038/s41598-021-86031-6





IMAGE OF THE MONTH

*Silent Spread: COVID-19 in Art*

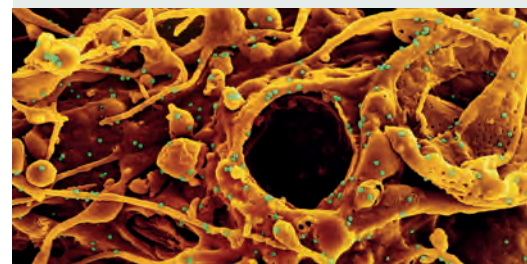
For the past year, artist Rebecca Kamen has worked with microscopists from the National Institutes of Health and other researchers to create a series of artwork that explores the concept of “corona” at both the micro and macro levels. The image above is a sneak preview of one such sculpture, but her new exhibition will also premiere a large wall-mounted installation, *Silent Spread*, that reflects and traces the migratory pattern of SARS-CoV-2 through 28 individual sculptures. The layout of this piece was inspired by an SIR diagram of COVID-19 and the decision to present it in monochrome was based on NIH/NIAID/RML scanning electron microscopy images of the virus.

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

QUOTE OF THE MONTH

“The success of LP-GC is an excellent example of a cooperation between three parties: academics who develop theoretical concepts, hardware developers that create the tools to put these ideas into practice, and users who re-define the workflows in their laboratory to maximally benefit from the new development.”

Hans-Gerd Janssen, in conversation with Jaap de Zeeuw and Steve Lehotay. Read the full story on page 20.



Dime-a-Dozen Diagnosis

A low-cost spectroscopy-based diagnostic could make fast (and accurate) COVID-19 testing more accessible

Current methods for SARS-CoV-2 detection rely heavily on RT-PCR – an admittedly highly accurate but costly technique that requires trained personnel and significant lab space – and it cannot be described as rapid. Now, researchers at Penn Medicine have developed a new smartphone-based test for COVID-19 that delivers fast results (within 4 minutes) with 90 percent accuracy.

Known as RAPID, which stands for real-time accurate portable impedimetric detection, the diagnostic test is built around electrochemical impedance spectroscopy (EIS), which transforms the binding event between viral spike protein and human ACE2 receptor into an electrical signal that can be read by a smartphone.

The test can be applied to both saliva and nasal samples, and is able to detect SARS-CoV-2 at low concentrations (1.16 PFU/ml). Perhaps just as importantly, it is also cheap and easy to produce; the electrodes can be mass-produced using screen-printers, meaning the entire test costs just \$4.67. High-frequency testing, particularly in remote and disadvantaged areas, has never looked so likely.

Reference

1. Penn Medicine News (2021). Available at: <https://bit.ly/35F7twxc>

A Question of Quality

Pharmaceutical analysis – driven by quality control – exists to assure both the safety and efficacy of drug products. As the world begins to emerge from the clutches of the worst pandemic in decades, the role of the pharma industry has never been more visible – nor have its efforts been under so much scrutiny. Here, we present the results of the **Pharma Analysis & Quality Control Trends, Challenges and Outlook 2021 Global Survey**.

In early 2021 – still very much in the clutches of COVID-19, Merck approached The Analytical Scientist with plans to gather the thoughts of the people “on the ground” in pharmaceutical analysis and quality control. Their hope? To uncover the major trends and main challenges.

One survey, over 200 qualified responses, and more than a handful of video meetings later, we are pleased to be able to share the final report with you: tas.txp.to/062IPQC

To whet your appetite, we caught up with one of the minds behind the survey – Wayne K. Way, Global Strategy Pharma Analysis & QC, MilliporeSigma – to explore a few key findings from the report in more detail.

What were the motivations behind the survey?

We were already well aware that the pharma value chain has been rapidly evolving over the last 5–10 years – driven by several key trends: i) the emergence of biologics from a niche position to a more mainstream market, ii) the rise of partnerships and collaboration, which essentially represents a shift in the pharma development mindset, and iii) an increasingly diverse spectrum of organizations – from the large multinational

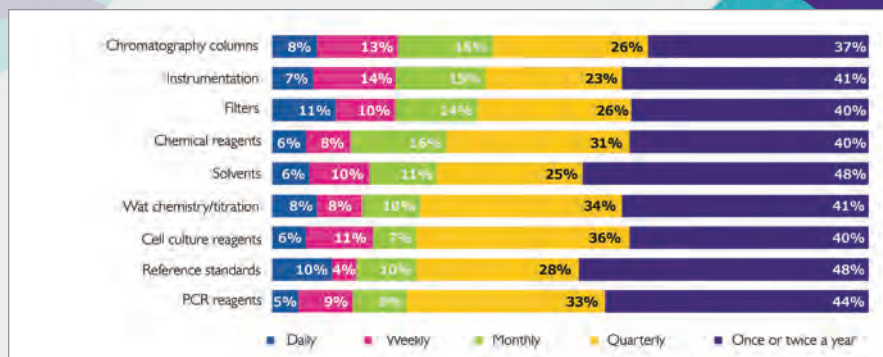


Figure 1. Survey respondents who faced reproducibility challenges shared how often different product groups cause issues.

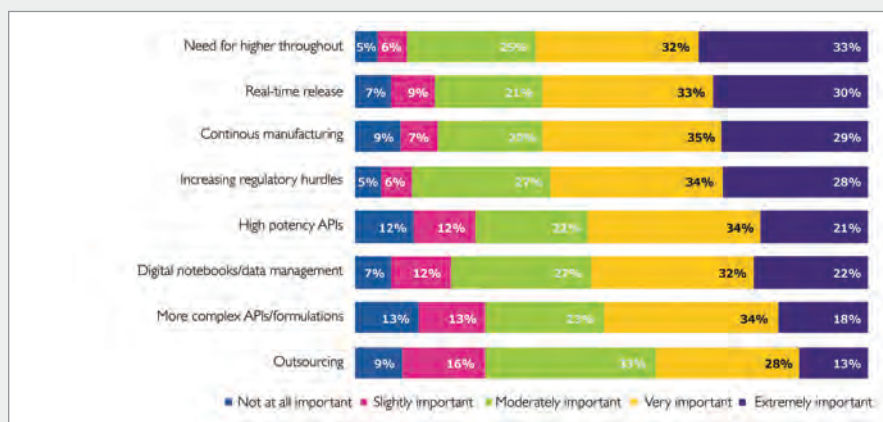


Figure 2. Survey respondents ranked the importance of key trends in pharmaceutical analysis and QC.

“big pharma” companies we know and love (!) to tiny biotech start ups with a single investigational new drug (IND).

Layered on top of those major trends in 2020 and 2021 is the COVID-19 pandemic, which has had its own influence in shaping current trends and driving new ones.

With so many trends and challenges pushing and pulling, it felt like a great time to grab our survey camera to take a snapshot of the industry as viewed by those in pharmaceutical analysis and QC. And though we are clearly interested in the results of the survey, our intent from the start was to create something that would have value for the industry as a whole – very much in line with the aforementioned trends of partnerships and collaboration.

Indeed, we also sought out an independent partner with a global reach – The Analytical Scientist – to help conduct the survey, analyze the data, and prepare the report.

Which survey result is most prominent in your mind?

What stands out most for me is the section on reproducibility and validation (see Figure 1).

In terms of reproducibility, there are evidently more challenges facing analytical labs than I initially suspected – and the issues don’t appear to stem from one particular tool or application. The frequency of reproducibility issues – daily and weekly for some respondents – was alarming.

In part, I was surprised by the results because they went against my own experiences in a pharmaceutical testing lab – admittedly 20 years ago (see “Meet Wayne Way”). Although we had our challenges and out-of-specification results, I don’t remember them happening that frequently – but maybe I am just remembering the good parts! Joking aside, I think the challenges likely reflect the increasing complexity of today’s drugs and

formulations – in particular, the increasing proportion of biotherapeutics – which inevitably leads to an increasing portfolio of potential problems. Method transfer from development to QC is also likely to be more challenging. Finally, time and staff pressure may be another driver. I was so interested in this section that I reached out to Michael Dong, Principal Consultant at MWD Consulting, for some perspective: “One of the significant challenges to the separation scientist is the efficient development of stability-indicating HPLC methods for the determination of diastereomers in multi-chiral new chemical entities (NCEs).”

Whatever the drivers, when I look at those results, I can only imagine the frustration...

We asked respondents to rank important trends affecting pharmaceutical analysis and QC – did the results (see Figure 2) meet your expectations?

When I look at the data, the top three – real-time release, the need for higher throughput, and continuous manufacturing – are all related to greater speed and/or efficiency – getting the drug out into the world faster. And that is not

surprising at all – especially as we try to manufacture our way out of a pandemic.

I was surprised by the fact that outsourcing ended up so low on the list; perhaps it's because it's not considered a “trend” as such but perceived as being in a steady state.

You'd already identified partnerships as a global trend; one survey question explored the types of partnerships organizations are engaging in – any surprises?

As you say, we knew partnerships and collaboration were important to pharma, but I was somewhat surprised by the scale presented in our snapshot!

The fact that a third of respondents partner with other pharmaceutical companies is good to see – and we've seen some very public examples of meaningful collaborations in the huge effort to vaccinate the world.

I was a little surprised to see vendors and suppliers so high up the list. Clearly, everyone has relationships with a number of suppliers – and it is rewarding to see that we have evolved from transactional exchanges to fully-fledged partnerships in people's minds.

The low ranking of contract research and contract development and manufacturing organizations (CROs and CDMOs) had us scratching our heads a little. But when we dug into the data, we found that CROs/CDMOs were more highly ranked by emerging biotech companies than by large pharma, which makes some sense. The relationship between pharma companies and CROs/CDMOs is complex, so we can only make educated guesses as to the reasons. But, for the bigger players, outsourcing a handful of analytical tests

Meet Wayne K. Way



After I received my PhD in analytical chemistry back in the mid-90s, I joined a small contract testing lab. At that time, the company didn't specialize in pharmaceutical services but that side of the business was growing, so the company decided to establish a dedicated division – in part because the industry was so strictly regulated. I led the team in that new division and we did all the work you might expect in an industry dominated by small molecules – including stability testing, method development, USP testing. And I also hosted my fair share of FDA audits, so I'm familiar with that experience...

After some years, I brought my pharmaceutical background and experience to Sigma Aldrich and then to MilliporeSigma, Bellefonte, PA, USA, an affiliate of Merck.

may be perceived more as a service than a partnership...

In hindsight, were there any questions you wished you had included?

It's always a balancing act to write a survey which is short and succinct to allow for easy completion but have the depth to actually realize meaningful results. In hindsight, I think we achieved this. If I had it to do over again, I would ask more questions around the trends, possibly digging deeper into automation and digitalization. Also, the issues regarding reproducibility and validation of products would be interesting, since the challenges in those areas seem larger than I expected.

Download the
Survey Report!

To download your free copy
of report, which also explores
partnerships, productivity
bottlenecks, budgets, and
more, please visit:
tas.txp.to/0621PQC

Pharma Analysis & Quality Control

Trends, Challenges and Outlook
2021 Global Survey Report

A collaboration between
The American Society for
Pharmaceutical Quality and Merck



The American Society for
Pharmaceutical Quality and Merck

Living in a Material World

Material choice is imperative to sample prep success; here are some of the key considerations that chemists must make – and why

By Verónica Pino, Professor of Analytical Chemistry, Chemistry Department and Researcher at the University Institute of Tropical Diseases and Public Health, University of La Laguna, Spain. Committee Member of the EuChemS-DAC Sample Preparation Study Group and Network.

There is no doubt that many of the current advances in sample preparation methods, particularly in the microextraction field, have taken place in parallel with those occurring in material science. As a result, a variety of novel solvents – such as ionic liquids, magnetic ionic liquids, and deep eutectic solvents, among others – have facilitated the development (or improvement) of several liquid-phase (micro)extraction methods. In the same manner, solid materials such as magnetic nanoparticles, carbon-based materials, metal-organic, and covalent-organic frameworks are starting to occupy a privileged position as efficient sorbents in many solid-phase (micro)extraction approaches.

The success of sample prep materials relies on designing and tailoring these materials to possess certain properties. Some properties are desirable for specific analytical applications. They can be tuned to be hydrophobic or hydrophilic, water-soluble or insoluble, with a modulable degree of porosity and surface area, with certain functional



In My View

Experts from across the world share a single strongly held opinion or key idea.

groups in their structures that facilitate further interactions with target analytes, and so on. The full list is very impressive indeed – and these materials can also be combined to form composites, giving further mixed or combined properties.

Another important aspect to consider when using novel materials in (micro) extraction methods is the resulting increase in the solvents and sorbents available to us. This expansion is clear and helps us to overcome limitations associated with traditional approaches. Additional characteristics of “greenness” are also associated with many novel

solvents and sorbents for extraction; these help us to develop more sustainable analytical methods. And if these reasons seem insufficient to recognize the impact of materials science in analytical chemistry, then consider the interest that such multidisciplinary work can provoke from other fields!

But we cannot be blinded by success; it is important not to lose sight of what must still be improved. Simply incorporating a material into an analytical method does not make it interesting or novel. The real questions we must ask when discussing novel

Experts in Reproducibility

*"We cannot be
blinded by success;
it is important not
to lose sight of
what must still be
improved."*


materials are: does the incorporation of the material improve the performance of the resulting analytical method? Does the material perform better than others (including commercial materials)? Is the proposed material truly green (if claimed) in terms of its preparation and potential cytotoxicity? Does it possess adequate inter-batch reproducibility? And, when using composites, is each individual component necessary? Was the complexity of the final composite really needed? If we do not pay due attention to these concerns, then we run the risk of missing our opportunity to improve the sustainability and performance of our approaches with novel materials. These considerations ensure that chosen materials are fit for purpose and provide us with workable results in a way that isn't detrimental to us or our environment.

Then there are also the questions we must ask beyond the remit of analytical chemistry. Were all materials properly synthesized and characterized? Was the yield reasonable? Was the preparation method affordable and sustainable? The list goes on.

Overall, decisions regarding the use of novel materials in sample preparation should be based in their design and selection for specific analytical applications. Sadly, this is often not

the case; much research opts to use any available material in seemingly random applications, irrespective of its suitability and design. It is our responsibility to adopt strong criteria in our studies rather than succumbing to research trends. We must not ride the bandwagon – we must guide it! We are visionaries and our expertise is invaluable. Let us use it for the betterment of our field – and our planet. And why not use the benefits gained to support other areas of research – say, material science – while we're at it?

Sample Preparation Study Group and Network belongs to the Division of Analytical Chemistry of the European

- 
- **RP-BioLC (U)HPLC**
 - **High Recovery IEX**
 - **Highly Efficient HIC & SEC**



Discover more at www.ymc.de

Chemical Society (DAC-EuChemS) and includes three working groups (WG): 1. Science and Fundamentals, 2. Automation, Innovation and Entrepreneurship, 3. Information Exchange and Networking.

The Sample Preparation Network welcomes new European and non-European regular members. Membership is open to individuals who subscribe to the objectives of the network and who are professionally engaged in or associated with sample preparation.

*For more information please visit:
<https://www.sampleprep.tuc.gr/en/home>*

Sample Preparation in Multidimensional Analysis



Innovative sample prep approaches often hide in the shadows of flashy new techniques – but it's time for them to step into the light

By Giorgia Purcar, Professor, Gembloux Agro-Bio Tech, University of Liège, Passage des Deportés 2, 5030 Gembloux, Belgium, and WG1 Leader of the EuChemS-DAC Sample Preparation Study Group and Network

Many analytical problems require high-performance techniques, especially when dealing with complex matrices

such as food products. Enhanced separation is often key to extracting the necessary level of information. This is true for both food quality and authenticity applications, where untargeted approaches are generally applied, and for food safety issues, where targeted and ultra-trace techniques are used.

Multidimensional separation techniques are popular in both of these settings (targeted and untargeted analyses). By coupling separation techniques, we can enhance peak capacity at each separation step, providing higher-level information (often multi-level) than single-dimension approaches. These multidimensional techniques often involve chromatography coupled to MS or other informative detectors.

The literature details plenty of fascinating and powerful approaches to increase the separation power of chromatography systems. However, the impressive development of such analytical systems in terms of sensitivity, selectivity, and separation power has led people to underestimate the role of sample preparation. It may be seen as an ancillary, undesirable, and time-consuming step. Many would rather opt for sophisticated and expensive instrumentation than spend valuable time optimizing and validating the sample preparation step.

The sample preparation community is very active in proposing brilliant and novel solutions. These include new sorbent materials and more rapid, miniaturized, and efficient purification methods, often with desirable “green” qualities. The potential of these new approaches is often not fully expressed due to the lack of analytical techniques powerful enough to support their evaluation and provide evidence to the wider community.

In short, sample preparation is

“A relationship even less investigated is the contribution of multidimensional chromatographic systems to the optimization of sample preparation steps.”

rarely regarded as an extra separation dimension that can contribute to the overall multidimensionality of a system. In this sense, sample preparation is a low-resolution technique that provides a limited additional peak capacity but often an essential contribution to the separation power of the process as a whole. Dedicated sample preparation can therefore simplify the overall analytical method by reducing our need for sophisticated instruments and increasing the power of an analytical method. This is particularly useful in the context of complex food matrices. I find it wild to think that any researcher would willingly (or perhaps, in some cases, unwillingly) pass up such a valuable opportunity to enhance their research capabilities.

A relationship even less investigated is the contribution of multidimensional chromatographic systems to the optimization of sample preparation steps. How? For instance, through the chromatographic separation of a

class of interfering compounds, thus reducing the need for extensive sample preparation steps. A good food-based example is the problem of mineral oil contamination, which requires both sophisticated analytical techniques and extensive sample preparation.

A closer interaction between multidimensional separation and sample preparation could increase the dimensionality of entire methods in a very dedicated and fit-for-purpose way – allowing us to reach higher and achieve more ambitious goals. Collaboration between these two inherently related communities will increase the amount of information extractable from any analytical method – in food analysis

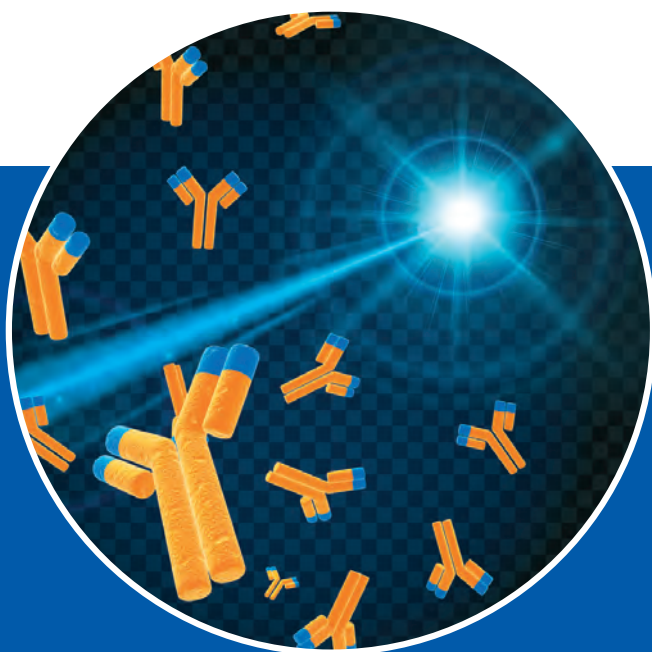
and beyond. In this context, the sample preparation community has created, within the Division of Analytical Chemistry (DAC) in EuChemS, a Sample Preparation Study Group and Network that aims to promote advances in the field and facilitate communication with other areas of analytical sciences. We hope that our DAC-EuChemS Sample Preparation Study Group and Network will play a fundamental role in building a fruitful alliance between sample preparation and multidimensional techniques. Together we will reach for the stars!

Sample Preparation Study Group and Network belongs to the Division of

Analytical Chemistry of the European Chemical Society (DAC-EuChemS) and includes three working groups (WG): 1. Science and Fundamentals, 2. Automation, Innovation and Entrepreneurship, 3. Information Exchange and Networking.

The Sample Preparation Network welcomes new European and non-European regular members. Membership is open to individuals who subscribe to the objectives of the network and who are professionally engaged in or associated with sample preparation.

For more information please visit: <https://www.sampleprep.tuc.gr/en/home>



PSS MAB^{NEW}

analytical and semi-micro SEC columns ideal for reproducible and comprehensive analysis of monoclonal antibodies with advanced detection



- PSS-made robust packing material in high quality hardware for long term reproducibility
- optimized pore and particle size for high resolution
- wide molar mass range, one column for analysis of mAbs fragments and aggregates
- designed and ready-to-use for light scattering detection

Laser Sharp Separations MAB SEC Columns

www.pss-shop.com



**PERFECT
SEPARATION SOLUTIONS**

www.pss-polymer.com
www.psscolumselector.com

Green Food Analysis: The Missing Link?

Green analytical chemistry principles could play an important role in helping us hit key sustainability goals – so what are we waiting for?



By Elena Ibañez, Research Professor in the Foodomics Laboratory at the Institute of Food Science Research (CIAL-CSIC), Spain.

I'd wager that most people have thought about the 2030 Agenda for Sustainable Development adopted by all United Nations Member States in 2015, as well as its 17 Sustainable Development Goals (SDGs) and how they can impact our world and humanity's future. Six years on, UN reports agree that we are not on track to achieve these SDGs by 2030. We can all make individual contributions, but strong and cooperative commitment at all levels is needed, including the upper echelons of science (1). The question I'd like to ask is: how can we push toward the SDGs in our everyday scientific work?

Our group at the Foodomics Laboratory has made attempts to implement the "Green Foodomics" framework in our research for some time (2). A lot has changed since we decided to integrate Green Analytical Chemistry (GAC) principles in our laboratory. We have modified our analytical methods to fulfill the GAC requirements, but preserved key qualities for method success, such as accuracy, sensitivity, reproducibility, simplicity, cost,

efficiency, flexibility, and speed. In this way, we achieve results of consistent merit, but with much reduced environmental cost.

In sample preparation, we have implemented new solvents and integrated extraction processes that are more benign in terms of energy and solvent consumption. We have also searched for solutions across omics platforms to help us determine food constituents and nutrients at molecular levels while protecting the planet. Green chemistry and GAC principles not only promote food security, but also help us strive for many of the individual SDGs, such as SDG 2 (Zero Hunger), SDG 3 (Good Health and Wellbeing), SDG 6 (Clean Water and Sanitation), SDG 7 (Affordable and Clean Energy), SDG 8 (Decent Work and Economic Growth), SDG 9 (Industry, Innovation and Infrastructure), SDG 11 (Sustainable Cities and Communities), SDG 12 (Responsible Consumption and Production), SDG 13 (Climate Action), SDG 14 (Life Below Water), and SDG 15 (Life on Land) (3).

Without any doubt, food analysis can drive renewed approaches in agricultural development, food processing, food security, nutrition, and health, thus promoting the sustainable development of nations. Moreover, GAC strategies promote not only safer, cheaper, and more sustainable analytical methods for food analysis, but also more affordable analytical procedures that can benefit society. Surely we would all benefit from these strategies in our day-to-day research!

Awareness of green chemistry and GAC principles in food analysis has increased exponentially in the last 10 years, with more than 80 percent of the publications including the terms "green chem*" and "food analys*" since 2010. I hope this awareness expands as we move forward. As Paul Anastas mentioned in his inspiring 1999 publication (4): "With knowledge comes the burden of responsibility. Chemists do not have the luxury of ignorance and cannot turn a blind eye to the effects of the science that

is created. Because there is the ability to develop new chemistries that are more benign, chemists are obligated to do so."

Therefore, researchers have a responsibility to be aware of the valuable links between green chemistry and success in food analysis. My take-home message: we know how we must proceed and we know what changes we must make. It is not only our duty, but also an invaluable opportunity to give a future to the generations that will come after us.

Sample Preparation Study Group and Network belongs to the Division of Analytical Chemistry of the European Chemical Society (DAC-EuChemS) and includes three working groups (WG): 1. Science and Fundamentals, 2. Automation, Innovation and Entrepreneurship, 3. Information Exchange and Networking.

The Sample Preparation Network welcomes new European and non-European regular members. Membership is open to individuals who subscribe to the objectives of the network and who are professionally engaged in or associated with sample preparation.

*For more information please visit:
<https://www.sampleprep.tuc.gr/en/home>*

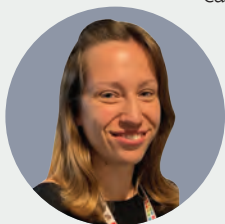
References

1. Independent Group of Scientists appointed by the Secretary-General, *Global Sustainable Development Report 2019: The Future is Now – Science for Achieving Sustainable Development*, (United Nations, New York, 2019). Last accessed June 15th 2021. Available at: <https://bit.ly/3xqqr5V>
2. B Gilbert-López et al., "Green foodomics. Towards a cleaner scientific discipline," *TrAC Trends Anal Chem*, 96, 31 (2017). DOI: 10.1016/j.trac.2017.06.013.3.
3. D Ballesteros-Vivas et al., "Green food analysis: current trends and perspectives," *Curr Opin Green Sustain Chem*, 100522 (2021). DOI: 10.1016/j.cogsc.2021.100522.
4. Paul T. Anastas (1999) *Green Chemistry and the Role of Analytical Methodology Development*, *Critical Reviews in Analytical Chemistry*, 29:3, 167-175, DOI:10.1080/10408349891199356.

A Collaborative Community for Everyone

The Royal Society of Chemistry (RSC) extends a warm helping hand to its members throughout their careers; we spoke with Jessica Evans to find out more...

Tell us about yourself and your role with the RSC
I studied chemistry at Reading then started work analyzing sports supplements. It was exactly what I wanted to be doing and I loved it, but I decided that a more people-facing role might be more suited to me. The RSC was an obvious choice from there, and the role of Membership Recruitment Executive suits me nicely! In addition to being part of a professional body in the field I'm passionate about, I'm also able to support other chemists flourish in their careers. I'll have been here for two years in July!



What makes the RSC so special?
I think many people will know us for our publishing work (we have 46 journals spanning the breadth of chemical sciences), but the RSC is known for a wide range of activities. What makes it so special? All of these activities are supported by our fantastic member community! And we also act as an advocate through our policy work. In the latter endeavour, we are striving to become even more active with bigger contributions to broad and important goals, such as increased diversity and sustainability. Our research campaigns – a prime example being “Breaking the Barriers,” which focussed on gender equity in academic publishing – are evidence of those efforts. Part of our royal charter is to maintain and enhance professional standards and

disseminate chemical knowledge – and all of this work supports that. We've been following our charter and empowering our members for over 180 years – and we're not stopping now!

Could you tell us more about the membership categories?
First is our student membership, which is available at a heavily discounted rate to give them the best start possible in their careers! Then we have our professional categories: associates, members, and fellows. Associate memberships are given to those who have just graduated or obtained an equivalent level of expertise through their working life to date; members have three years of post-study experience; and fellow-level memberships are given to those with at least five years of experience in a senior role. For people who don't yet have a formal qualification or the required years of experience, or who are otherwise involved in the chemical sciences, there's the affiliate category. Members of any category benefit from our support irrespective of their working sector.

How do you support your members through all stages of their careers?
Our members work in a fast-paced environment that constantly evolves. We recognize that professional development is key to career progression in this environment; professional awards offer a framework to ensure that members develop their skills and knowledge in a rounded and effective way. Chartered Chemist, Chartered Scientist, Chartered Environmentalist, Chartered Manager and the Professional Registers are awards that highlight important soft skills and facilitate continuous development at every career stage.

Then we have our mentoring scheme and peer support groups – designed to help our members share experiences and guide one another. But we're constantly developing

our offerings! For example, a new hub that offers guidance for interviews and preparing CVs, as well as self-assessment tools, will be available to our members soon (watch this space).

Do you receive any positive feedback on your offerings?
We collect feedback through annual surveys – and the results are overwhelmingly positive. In 2020, 92 percent of responding members said they were proud to be a member! And 91 percent agreed that we are advancing excellence in the chemical sciences. Of course, we also receive some constructive criticism – we value this just as much as the positive feedback as it helps us to remain relevant and ensures that we can continue being a diverse and inclusive community in the chemical sciences.

Nessa Carson, a member and senior automation scientist at Syngenta, also provided this great feedback about our careers services: “When people ask me why they should join the RSC, I always tell them about the amazing career advice. I think a lot of people forget that careers support is part of your membership, but it totally is and you can talk to the team at any time you like.”

Great feedback! And what else would you say to somebody thinking about joining?
I'd tell them that we provide support for everyone – no matter their career stage, sector, or location. And, more than that, we offer a welcoming community that encourages conversation and collaboration between talented and like-minded individuals. Community is what we're all about – and our members seem to agree! After all, 77 percent of them said that they felt that they “belonged” with the RSC in our 2020 survey.

To hear more about our members' experiences, please visit our website (rsc.li/memberstories) or tune in for one of our monthly Instagram or Twitter live sessions. I'm having a blast chatting to the attendees and I look forward to seeing you there!

Native LC-MS: From the Lab to the Manufacturing Floor

How is the characterization of non-denatured biomolecules driving scientific progress in industry and academia?

The use of native LC-MS has grown significantly in the last decade. But what continues to make this tool so useful for professionals in academia and industry? Heidi Vitrac, an Applications Scientist at Tosoh Bioscience, and Rob Haselberg, an Assistant Professor at the Vrije Universiteit Amsterdam, share their perspectives on the technique, and explain why it suits the needs of the curious minds behind blue skies research, as well as the practicalities of biopharmaceutical manufacturing.

What is “native” LC-MS?

Heidi Vitrac: Native MS refers to the process whereby large biomolecules and complexes can be transferred from a three-dimensional, functional existence in a condensed liquid phase to the gas phase via the process of electrospray ionization (ESI). Native MS allows solution state non-covalent protein interactions to be maintained in transmission into the gas phase of the mass spectrometer. When hyphenated with LC, native LC-MS refers to the analysis of biomolecules in their native, non-denatured state.

There has been a steady increase in the use of native LC-MS over the past 10 years, largely driven by the development and expansion of high-resolution mass spectrometers from various vendors. Setting up instruments and running native MS experiments is not as daunting a task as it was twenty

years ago; back then, scientists had to build and customize their interfaces to perform fit-for-purpose analyses. We've also seen huge amounts of progress in the development of software and resources to support such analyses, significantly accelerating and simplifying data processing. Altogether, native LC-MS has become a much more approachable technique that even scientists with little MS training can use.

In which applications does the technique shine?

Rob Haselberg: In a biopharmaceutical context, native LC-MS helps provide a better understanding of proteins. Take monoclonal antibodies (mAbs), for example; their behavior can be analyzed on a molecular level – helping to determine how quickly they bind to receptors and providing insight into their physicochemical properties. There's a lot of information that can be extracted with the native LC-MS approach.

Vitrac: Thanks to various improvements in sensitivity, resolution, and mass accuracy of mass spectrometers, native LC-MS is now routinely used in many pharmaceutical and biotechnology laboratories for the analysis of mAbs and other protein therapeutics to assess purity, and profile antibody glycosylation. But the technique is not restricted to protein analysis. It can also be applied to macromolecular complexes, including drug-macromolecular complexes, lipid-protein interactions, and DNA-protein interactions. By preserving the native structure of the biomolecules of interest, native LC-MS allows us to determine the mass of intact assemblies, their precise stoichiometry, direct interactions between subunits, and the strength of inter-subunit interactions.

Can other technologies achieve the same goals?

Haselberg: Put simply, no! Of course,

bioassays can be used to determine some of the functional characteristics of biomolecules, and surface plasmon resonance can help paint a picture of a molecule's binding and affinity kinetics, but native LC-MS provides additional insights – and much faster. Using this approach, you can quickly decipher the high-order structure of a given molecule as well as the covalent complexes it forms. And the basic architecture of a molecule can easily be revealed with native LC-MS.

What specific challenges does native LC-MS present?

Vitrac: The hyphenation of LC with MS is quite different from any other optical detector. The biggest difference pertains to the need to switch from the liquid phase to the gas phase, which is achieved in the ion source of the MS instrument. And that makes optimization of the mobile phase used in the LC separation a critical component to the method development process. And because native LC-MS often happens under physiological conditions (i.e., neutral pH), you cannot use organic solvent or acid in the mobile phase, which adds to method development challenges. Notably, native LC-MS is not restricted to size exclusion chromatography; indeed, several other modes of chromatography can be used in combination with native MS, including capillary iso-electrofocusing (cIEF), hydrophobic interaction chromatography (HIC), and anion exchange chromatography, as recently demonstrated for various mAbs.

Can native LC-MS be further improved?

Haselberg: Sometimes the practical questions we have are greater than the technology practically allows us to explore. So, compromises between separation and detection may occasionally be needed. From an academic point of view, flow rate and

Meet the Experts



*Heidi Vitrac, Applications Scientist,
Tosoh Bioscience.*

"I obtained my PhD in Physical Chemistry at Paris Descartes University and quickly developed an enthusiasm for cross-disciplinary studies around analytical biochemistry. In 2008, I moved to the US and joined the University of Texas Health Science Center at Houston. I enjoyed taking on challenging projects and contributing to the advancement of collaborative work. And that's what led me to join Tosoh Bioscience in December 2020. With Tosoh Bioscience, I contribute to the development and optimization of analytical methods and processes for the separation, identification, and characterization of various biomolecules."



*Rob Haselberg, Assistant
Professor, Faculty of Science,
BioAnalytical Chemistry,
Vrije Universiteit Amsterdam*

"I received a master's in analytical chemistry from the Vrije Universiteit Amsterdam in 2006 before moving on to my PhD, which focused on the characterization of biopharmaceuticals using a combination of capillary electrophoresis and MS. I've always been interested in biomolecular analysis and, drawing on that passion, I now work in the VU's BioAnalytical Chemistry group, where much of my research is geared towards understanding native protein characterization."

spectrometer compatibility also have to be considered. But working with a competent vendor can make a huge difference in how greatly these factors impact research.

Vitrac: From my perspective, the biggest needs are related to data interpretation. Biomolecules are complex and teasing apart the information on each component of the complex from a series of mass spectra remains challenging. Data processing software has improved enormously for biotherapeutics, but further development will help us better understand "out-of-the-ordinary" complexes.

Where does Tosoh Bioscience fit in?

Vitrac: We have accumulated a wealth of experience in the development of chromatographic methods – and we are happy to help optimize any separation. From academic environments to big pharma, our chromatography experts can support the growing needs of our customers. As proven specialists in the field, we work with biopharma partners at all scales – from UHPLC analysis to purification at the manufacturing scale. Any customer with a separation problem can simply contact us; we will take the time to listen and to understand the issue before finding the best solution.

Haselberg: As a lead member of an analytical chemistry group, I work on improving hardware. For example, our group often requires columns that can manage low flow rates, so working with a company like Tosoh Bioscience – who truly understands our scientific needs – is great. They also host user meetings, where we can share our data and any challenges that we have encountered. These sessions are always useful as they share practical solutions with us too. We have had an enduring collaboration with the company – a testimony to the services it provides!

What's next for biomolecular characterization?

Haselberg: I predict that we'll see an increased use of affinity columns that incorporate the power of mass spectrometry in coming years. Why? Because it will enable us to purify and characterize molecules in a single system. I also think we will see more multidimensional chromatography, including hyphenation, that will help deepen our understanding of biomolecules. These techniques will help overcome some of the compatibility issues we face today.

Vitrac: Like Rob, I am interested in seeing how multidimensional chromatography can be used in native MS analysis. It has the potential to create powerful pipelines where the quality attributes of any given biomolecule can be assessed during the various stages of downstream processing. I am also curious about new applications beyond protein therapeutics and complexes. I look forward to seeing the next jump from academia to industry, especially regarding the analysis of DNA and RNA molecules inside complexes. One thing is certain: our team is truly invested in the success of our customers' work, so we will continue to find new ways to work together to take biopharmaceutical research to the next level.

THE (LONG AND WINDING) ROAD TO LPGC - MS

Jaap de Zeeuw, Hans-Gerd Janssen, and Steve Lehotay recall the origins of low-pressure GC, highlight the hurdles that arose during development, and discuss its relevance today.

LPGC, when coupled to MS, is a fast and robust alternative to traditional GC-MS – but the concept of LPGC is not new; in fact, the low-pressure route towards faster GC has been known to analytical chemists since the 1960s. However, several challenges have stood in the way of its widespread adoption. In 2000, Jaap de Zeeuw injected (no pun intended) new life into LPGC with a simple solution – a restrictor that maintained positive inlet pressure for a wide-bore column.

Advocates of the technique have had to navigate a long and winding road fraught with obstacles, including technical challenges, commercial pressures, and dismissiveness from

the analytical community. Today, LPGC-MS is accessible to all via a commercialized kit.

Here, three trailblazers on LPGC's journey – Jaap de Zeeuw, Hans-Gerd Janssen, and Steve Lehotay – share how the technique managed to persevere despite the hurdles and discuss where it might go next.

Disclaimer: Mention of brand or firm name does not constitute an endorsement by the USDA above others of a similar nature not mentioned. Lehotay's views in this article are solely his own and do not represent the views or position of the USDA or any other entity.



When did you first encounter LPGC?

Jaap: I guess I should kick this one off! The idea first occurred to me in around 1997 when I was thinking about MS and how it commonly uses long 0.25 mm columns. This is a logical choice when you need positive pressure in the injection port and the MS is running under vacuum – you need that length to have sufficient restriction. But, as I'm always looking for a challenge, I wanted to see if it was possible to use a wide-bore column with MS rather than the typical narrow-bore.

Based on the Van Deemter equation, I realized that – theoretically – at lower pressure a much higher optimal linear velocity could be obtained. I checked the literature for vacuum GC but saw that the setup being trialed was often challenging because the vacuum had to be created in the injection system. Instead, I proposed using pliers to restrict the flow on the inlet side of a metal 0.53 mm i.d. capillary. This approach led to a similar separation but an approximately nine times faster run time – and that simple idea was the basis of what we've continued to build upon with LPGC-MS to this day!

Steve: Let's see, my first email to Jaap was on February 25, 2000 – I had come across the title of a presentation that he made in Gifu, Japan, in November 1999, and Aviv Amirav had given me Jaap's contact info. In the email, I described how I had already made plans for a summer student, Katerina Mastovska, to investigate LPGC-MS with a quadrupole MS instrument. Interestingly, though, I first heard about "subambient pressure GC-MS" in 1989 from Mark Hail of Richard Yost's group at the University of Florida when we were both graduate students there.

"BASED ON THE VAN DEEMTER EQUATION, I REALIZED THAT – THEORETICALLY – AT LOWER PRESSURE A MUCH HIGHER OPTIMAL LINEAR VELOCITY COULD BE OBTAINED."

Hans-Gerd: Well, the general concept has been around for a while – Carel Cramers, Piet Leclercq, and Jack Rijks started research into speeding up GC separations at Eindhoven University sometime in the 1970s. Cees Schutjes, the first PhD student in the field, defended his thesis in 1983, which included a theoretical treatise of the Golay equation. From this equation the increase of the mobile phase diffusion coefficients immediately followed as one route towards faster GC. When I started as a student in the Cramers' group in 1986, the thesis of Schutjes was standard information we all had to study. We also studied vacuum outlet conditions for their higher speed. But it was only around 1998 that we started doing experiments in low pressure GC, jointly with Jaap.



Meet the LPGC Experts

Jaap de Zeeuw is currently an international specialist in GC at Restek Corporation. With 41 years of experience in GC capillary technology, he has developed many PLOT columns, developed the first bonded wax column, published more than 100 articles in the field of GC, and is the inventor of fast low-pressure GC using restriction at the inlet. Jaap also made the world's longest fused silica capillary, for which a Guinness World Record was granted. In 2016, he developed a new technique for coating PLOT columns based on SPIN deposition. Jaap has several hobbies, such as gardening, playing music, scouting, and helping out with his wife's B&B, and he is currently working on a program for teaching creative thinking to technical/analytical people.



Hans-Gerd Janssen has an MSc and PhD degree in analytical chemistry from Eindhoven University where he studied and later worked in Carel Cramers' group. After working at Eindhoven University for almost 10 years as assistant and associate professor, he joined Unilever in 1999. Janssen has written more than 200 publications on theory and method development in chromatography and MS. From 2004 to 2019, he was a part-time professor at Amsterdam University, next to his position as senior scientist in analytical chemistry, focusing on food analysis, at Unilever R&D Wageningen. In 2019, he accepted a part-time professorship at Wageningen University where his research focuses on recognition-based analytical chemistry. Janssen holds positions in the editorial advisory boards of several journals and has served in various scientific and organizing committees for international conferences.

Steven J Lehotay is a lead scientist with the USDA Agricultural Research Service at the Eastern Regional Research Center in Wyndmoor, Pennsylvania, USA. Since 1992, he has conducted scientific investigations and method development research involving improvement in the analysis of pesticides, veterinary drugs, and other contaminants in food and environmental samples. Steven is the co-inventor of the "quick, easy, cheap, effective, rugged, and safe" (QuEChERS) sample preparation approach. And he has been awarded with numerous honors, including the AOAC International Harvey W Wiley Award. According to the Stanford c-score metric, he resides among the top 0.19 percent of published analytical chemists.



Did you immediately recognize the benefits of this technique?

Steve: I've always felt fortunate that I learned chromatography from John Dorsey at the University of Florida at the time. Being a great teacher, Dorsey always started each chromatography class with questions about his previous lecture. After spending weeks on the theory of chromatography with an emphasis to optimize separations and peak resolution, Dorsey began class one day by drawing a chromatogram on the chalkboard of two peaks with excellent resolution about two minutes apart. He then asked, "What's wrong with this separation?" He brushed aside the aspersions that his drawn peaks weren't perfectly Gaussian, and no one in the class saw a problem. He announced, "It's wasting time!"

I've never forgotten that moment or that concept, but it seems too many others have. I think too many chromatographers and mass spectrometrists forget that we are all *analytical chemists*. The specialist's mindset fixates on the power of chemical separations and not enough on practical matters of sample preparation, throughput, ease, cost, ruggedness, validation, and – above all – robustness. When I learned about Rapid-MS in 2000, I knew immediately that the restriction capillary was a brilliant idea and a solution for fast GC-MS. Having entered the "real-world" of pesticide residue monitoring in 1992, I recognized the benefits of LPGC very quickly. I was taught to always use a guard column in chromatography, and the idea to use the guard column also as a restrictor in LPGC was an elegant solution that I wish I had considered first!

Jaap: I immediately recognized the value of LPGC-MS, but some of those around me did not initially. Once I came up with my "simple solution," I proposed the idea to the management of Varian – the company I was working for at the time. They didn't take interest at first, so I wasn't able to do any experimentation. I then spoke to some of my esteemed colleagues – namely Carel Cramers, Aviv Amirav, and Hans-Gerd Janssen – and Varian became more interested with this expert backing. However, they decided it was more of an "academic" pursuit best left to the University of Eindhoven, and this is when Hans-Gerd and I began working together.

The initial protocol, based on the 0.53 mm capillary that had to be squeezed on one side using pliers, seemed really promising so we eventually filed for a patent – the initial design used a short 0.10 mm ID restriction (ca. 60 cm) coupled with a 10 m x 0.53 mm capillary. We worked with over 20 external groups who all came back with results showing the speed benefit of the columns. On top of this, it

was clear that the technology would fit into many different application areas.

At this point, Varian took ownership of the product and decided to introduce it exclusively for the ion trap MS, with application in environmental trace analysis of pesticides and PCBs.

I think this was a mistake – it took three years before this "Rapid MS" offering was also made commercially available because it didn't gain the expected revenue. Notably, the Rapid-MS instrument had a slower data acquisition rate than others, and I think this put a lot of people off.

Hans-Gerd: It's a good point Jaap makes here. The larger instrument and column manufacturers are sometimes a bit risk averse, so even though Varian eventually recognized the value of LPGC, it took a while to develop. Generally, I think the larger companies try to target scientists at conferences and hope that they will start to use the new technology and spread the word. That works, but is not a rapid route.

At Eindhoven University, we always had a massive interest in fast GC. Over the years we have helped many labs convert their regular GC to a faster run. Although we were mostly following the route of narrow-bore columns, it was clear that other options like very short columns, columns packed with very fast particles, or low-pressure outlet conditions also

had their unique advantages. LPGC was always an option that people liked because it required only very small modifications to the equipment. Sometimes narrow columns are the preferred route, sometimes LPGC is better, sometimes both approaches work. But I'd say we very much recognized the benefits of LPGC-MS when it came along.

"I IMMEDIATELY RECOGNIZED THE VALUE OF LPGC-MS, BUT SOME OF THOSE AROUND ME DID NOT INITIALLY."

What additional developments led to the technique as it is today?

Jaap: In the first three years, there was a lot of noise in the market. Lots of people saw its potential and wanted to experiment with it – one such person in particular was Steve. During this period, I recognized some limitations in terms of the restriction lifetime/maintenance and the coupling, but never got the chance to work on that at Varian. However, when I joined Restek in 2008, I finally had the opportunity to try out different ways of making the restriction.

I came up with another simple solution based on making the coupling with PressFit and positioning this inside the injector body. This meant the coupling and restriction were always at high temperature and in an inert atmosphere. A publication was written and patent filed, but it never made it to a commercial product.

Steve: My colleagues and I had issues with the very narrow restriction capillaries in the Rapid-MS product. We ended up simply connecting two commercially available columns from any vendor (5m, 0.18 mm i.d. guard/restrictor capillary with a 15 m, 0.53 mm i.d., 1 μ m film thickness analytical column), which provided both more robustness and theoretical plates. I reached out to all the GC vendors for 20 years about LPGC, and in 2021, Restek finally commercialized a product using our column dimensions.

Aside from this, there have been many technological advances in the past two decades to continually improve upon the performance and features of LPGC-MS. Most notably, commercial triple quadrupole MS/MS instruments were introduced, which provided greater targeted analyte detectability (both sensitivity and selectivity) and faster data acquisition speeds. High-resolution MS instruments have also been introduced, for which LPGC is compatible. Improvements of QuEChERS and analyte protectants streamlined sample preparation and improved peak shapes in GC. The development of a light and reliable capillary column union also helped make LPGC more practical for shipping and installation.

Who should consider LPGC-MS?

Steve: I think everyone that is using GC for analysis should consider LPGC-MS. My lab has used it routinely for nearly 20 years now. Why? Firstly, megabore columns are preferable in routine monitoring using GC because of their much greater sample loadability and robustness. LPGC is therefore very useful for rapid, sensitive, and robust analysis of pesticides, environmental contaminants, and pretty much any GC-amenable analyte that isn't too volatile. Secondly, LPGC as a product can be used as is in general applications, but, as a technique, it also possesses more parameters for investigation

and innovation than standard GC-MS. For example, Amirav, Fialkov, and I recently published a paper (1) using resistive heating in LPGC-MS with a short 0.25 mm i.d. capillary column that achieved multiresidue analysis in <1 min. My long-term research plans are to implement such methods to enable ultra-fast monitoring without having to ship samples to a lab, for example. In the short term, one of my projects is to systematically evaluate LPGC-MS in food safety applications using different column dimensions.

Jaap: What we basically do with LPGC is trade efficiency for speed, but using a robust solution. As long as components that elute at the same retention time can be separated by MS, LPGC is useful. Of course, if isobaric components elute together it will not work. In that case, we need separation by chromatography using highly selective stationary phases, or use other means, such as software tools, to meet the analytical need.

It's also worth noting that there are other ways to speed up MS separations, like working at higher flow, extreme fast programming, and using short, smaller diameter capillary columns. But these do not provide the robustness and loadability of the vacuum GC solution.

Hans-Gerd: LPGC is not unique – it is one of approximately 10 routes towards faster GC. But it is a rather simple technique. In generic terms, I would think it is the preferred method if you have simple separations not requiring a high peak capacity and are using MS detection, while sample preparation is not too much of an issue. In such situations, LPGC can increase your sample throughput up to five or ten-fold.

So why haven't more people adopted LPGC?

Hans-Gerd: It's a good question, and we have to be honest here. We clearly thought that all labs would move to faster GC, but nowadays we see that the vast majority of them are still using the classical columns with run times between 30 and 60 minutes. I see two reasons for that. First, I think the need for very fast separation is limited. With a regular run time of say 45 minutes you can easily do 30 samples per day. Many labs will not have that many samples.

“A DRAWBACK OF
LPGC IS THAT
YOU NEED TO
BUY A SPECIAL
“THING;” THE
RESTRICTOR. A
BIG STEP FORWARD
WOULD BE LPGC
WITHOUT THE NEED
FOR A RESTRICTOR
AT ALL”



And we should also not forget that the sample preparation, data interpretation, and paperwork that comes with 30 samples per day can be significant. The GC run itself is usually not the rate-limiting step, and for many the benefits of faster GC are simply not worth the investment and risk.

A second reason for the limited acceptance of fast GC is the strong overpromise in literature and by some manufacturers. With fast GC there is always a price to pay. Narrow-bore columns offer you a faster analysis speed at the expense of a slightly reduced system reliability. LPGC only works for simple separations. Fast temperature programming reduces your separation power a lot. These limitations have not always been communicated honestly.

Jaap: As I've mentioned, some were slow to recognize the value of this technology and I think this has been the biggest limiting step to progress. Even when people (or instrument companies) did recognize the benefits of LPGC, they couldn't see the value in pursuing it commercially. In particular, Varian didn't fully recognize the impact of LPGC having low data acquisition rates.

Steve: Right. Varian made the initial mistake of treating Rapid-MS more as an "introduction device" to their ion trap MS detector, which was not ideal for LPGC due to its slow (250 ms) data acquisition rate. Secondly, the product was introduced before it was fully studied and optimized, leading to narrow marketing and less-than-ideal column dimensions. Another crucial mistake was the over-pricing of the product. Justifiably, the primary goal of a company is to make money – meeting customer needs is only pursued if it serves this primary goal – but if more customers had demanded LPGC, then vendors would have taken more notice. Even so, the 20-year time frame of Jaap's US patent held by Varian and then Agilent certainly put a dampener on commercialization by others until now.

Hans-Gerd also makes good points. Furthermore, LPGC does not work for MS techniques that do not operate with the ion source under vacuum conditions. Also, many volatiles are already analyzed quickly in standard GC, thus LPGC is not going to provide as much gain compared to analyses that currently take 15–60 min. Otherwise, LPGC-MS trades a small degree of separation efficiency for speed, sensitivity, and robustness.

Misaligned incentivization is another problem. For example, nearly all academicians choose to study what rewards and/or interests them the most. The "novelty" of the idea and technique usually motivates them, and they tend to seek applications to suit their preferred tool, not the other

way around. Grants, patents, and citations usually drive their choices. Company scientists are similar in that they spend an inordinate amount of their time on niche applications that are difficult for those customers who complain the most loudly. In my view, they should put more focus on improving efficiency and performance of their most profitable applications that are taken for granted. Moreover, the scientific publishers and media tend to highlight "sexy" topics, which are promoted by those scientists on their editorial boards.

I can give several other reasons more people haven't adopted LPGC. There have been informed criticisms over the years, such as the need for more separation efficiency, analyses of volatiles, or problems with column bleed. But one of my biggest frustrations is to notice dismissiveness, disbelief, and disinformation from those who have never studied or tried LPGC themselves.

What would you like to see for the future of LPGC?

Jaap: In theory, the technique could allow even faster separations depending on the temperature programming speed of the instrument. The 15 m column chosen here could also be replaced for a shorter column – like a 7 m x 0.32 mm or even a 3 m x 0.25 mm column – as long as vacuum conditions inside the separation capillary are created. However, there will of course be other challenges for using such short capillaries, including sample introduction and focusing.

Steve: Do you know what may be even better than LPGC-MS? Fast GC-MS using supersonic molecular beams (SMB) – also known as "Cold-EI." In SMB-MS, the column outlet is not under vacuum, thus LPGC is not possible using that detector. However, column flow rate can be increased to 32 mL/min, for example, to provide rapid, high-quality analyses. I would urge anyone in this field to view the application notes and publications from Aviv Amirav. His long and winding road has also been fraught with multiple bad timings (company consolidations) and human foibles.

Hans-Gerd: A drawback of LPGC is that you need to buy a special "thing;" the restrictor. A big step forward would be LPGC without the need for a restrictor at all. This would require the gas inlet system of the GC to be able to work with sub-ambient pressures while still avoiding the ingress of air via the split exit – but it should be technically feasible.

Also with regards to the future, Steve's work on faster integration methods (summation integration) should be mentioned. The

“IT SHOULD BE OF INTEREST TO ANYONE USING MS, IN MY OPINION, BUT THE BEST WAY TO GET THE WORD OUT THERE IS TO SHOW THE DATA AND LET EXPERIENCED CHROMATOGRAPHERS SPEAK UP.”

GC run time might be relevant for the total duration of your analysis, but in terms of costs it is not the main contributor. LPGC combined with simpler, fully automated, and more reliable methods for peak integration is an ideal combination.

Steve: Thanks for mentioning the summation function integration. Indeed, you are right to point out some of the drawbacks of LPGC, so I want to summarize how we've been overcoming the current limitations of this technique: i) we have done high-throughput and easy sample prep with QuEChERS (and now QuEChERSER) since 2003; ii) we also have been using analyte protectants since 2003 to improve peak shapes and separations for somewhat polar analytes; iii) for the past decade, we've been increasing selectivity of detection by using MS/MS (for targeted analytes only); and iv) since about 2015, we've used summation integration (for targeted analytes only, too).

You also mentioned the “thing” needed for LPGC – that “thing” is merely an appropriate guard column and union, which are not unusual items. I suppose ferrules for the megabore column is another “thing,” but standard columns, liners, septa, ferrules, nuts, and so on are also “things” that by the same logic should preclude anybody from doing any analyses at all! In any case, Restek now sells that “thing” in the same way as any other item, and LPGC has always been available as a custom item.

Hans-Gerd: Excellent remarks Steve! And it's this type of discussion that highlights, I believe, our passion for this often overlooked technique. I know only a few users of LPGC, but I am not aware of anyone who tried it and gave up. The technique works and is reliable and there are certainly more people who could benefit from it.

Jaap: I couldn't agree more. Essentially, LPGC-MS can speed up a lot of conventional MS applications where analysis time is important. It should be of interest to anyone using MS, in my opinion, but the best way to get the word out there is to show the data and let experienced chromatographers speak up.

Steve: As hundreds of people involved in GC analysis can attest, I have discussed LPGC in nearly every encounter with them for more than 20 years! My inclusion of a few slides about LPGC has been a staple in most of my presentations, to the point that some people are sick of hearing about it (and I am definitely sick of talking about it!). I've emailed many gurus of GC over the years about LPGC, and when I noticed research or review articles in which LPGC should have been mentioned, I sometimes emailed key publications about LPGC to the authors to inform them of their oversight.

As a US federal civil servant, I have no business or financial relationships with anyone about my work, and my motivation is to help others improve their chemical analyses and lab operations. I admire Jaap de Zeeuw for inventing the restrictor approach, and I've wished for 20 years that my lab could simply purchase pre-connected LPGC columns with the dimensions of our choosing. Now that this option is available, there is one less excuse for those who haven't tried LPGC-MS.

Hans-Gerd: This has been a trying journey, that's for sure! But we've all come away from it having grown and developed as analytical scientists along the way. For us, the success of LPGC is an excellent example of a cooperation between three parties: academics who develop theoretical concepts, hardware developers that create the tools to put these ideas into practice, and users who re-define the workflows in their laboratory to maximally benefit from the new development. Many successful new methods are the result of such three-party interactions.

Reference

1. A Fialkov et al., *J Chromatogr A*, 1612 (2020). DOI: 10.1016/j.chroma.2019.460691

A Herbal (Fraud) Remedy

Deploying the Thermo Scientific Orbitrap Exploris GC MS System in the fight against adulterated oregano

By Giulia Riccardino, Senior Applications Specialist, Thermo Fisher Scientific

Adulteration of oregano can be accidental or intentional – the latter being driven by price and demand. Leaves from other plants (for example, olive, thyme, marjoram, sumac, myrtle, and hazelnut) are frequently used as adulterants because they are difficult to detect via visual inspection. Whatever the mode of adulteration, the fight remains the same: to ensure products are authentic and safe. Here, we take a look at the capability of the Thermo Scientific™ Orbitrap™ Exploris™ GC 240 mass spectrometer to solve this age-old problem.

Quality odors

Oregano has a diverse composition of phytosterols, pigments, and essential oils – complexity that can make analysis challenging. But by applying the powerful combination of GC and high-resolution accurate MS (GC-HRMS), analysts can explore the volatile organic compounds (VOCs) – a new window through which to assess purity. Indeed, the approach provides full-scan data acquisition together with high sensitivity, high resolution (240,000 FWHM), and accurate mass determination (<1 ppm).

Furthermore, GC-HRMS is compatible with the headspace solid-phase microextraction (HS-SPME) technique (1), which permits a simple, one-step extraction and concentration of oregano's volatile organic compounds (VOCs) – mainly monoterpenes and sesquiterpenes. By comparing test and reference sample

profiles, we can detect and identify even very low-level contamination or sample profile constituents. Depending on compound type, these differences could be in the parts per billion (ppb) level.

The simple sample preparation associated with HS-SPME is a critical factor in non-targeted analysis, as each successive manipulation can alter the sample composition (2), thereby confounding analysis. Finally, the GC-HRMS full-scan data acquisition capability supports targeted, non-targeted, and retrospective data analysis (1), underscoring its broad applicability.

Proof of the pudding

We assessed the power of the GC-HRMS approach by analyzing the aroma profiles of native oregano alongside oregano samples that had been adulterated to simulate fraud. Using the Orbitrap Exploris GC 240 system, we compared full-scan total ion chromatograms (FS TICs) for native oregano, native thyme, and oregano adulterated with a thyme constituent. Our method clearly discriminated between native and adulterated samples: differences related to the prevalence of i) odor components common to both thyme and oregano (for example, thymol, which is present in the aroma of both oregano and thyme, but at different abundances); and ii) odor components specific to either oregano or thyme.

The peak differences could be visually identified on the TIC readout, but were also analyzed statistically. Statistical analysis tools included Thermo Scientific™ Compound Discoverer™ software (used for PCA analysis, which highlights variation between sample groups) and volcano plots ("V-plots," used for identifying changes in large datasets

comprising replicate data). These methods highlighted quantitative changes in aroma components and identified compounds not typically associated with native oregano, thereby permitting discrimination between native and adulterated oregano.

Time to explore?

With the Orbitrap Exploris GC 240 system, food manufacturers can assure the quality of supplies with unmatched efficiency, rigor, and confidence. Orbitrap

Exploris GC systems permits rapid change-over from EI (for spectral library search) to softer ionization (for example, PCI, for confirming molecular ions through the use of adduct information). The system also has the capability to perform accurate MS/MS experiments (for structural elucidation). Quality of herbs,

such as oregano, can be assured by analyzing the aroma profile with principal components analysis and differential analysis. Finally, Orbitrap Exploris GC comes with the FreeStyle elemental composition calculator and Thermo Scientific™ Mass Frontier™ Spectral Interpretation software for predictive fragmentation and structural elucidation. All together, these features enable compounds to be identified with unprecedented ease and confidence.

References

1. M Diaz-Maroto, et al., "Headspace solid-phase microextraction analysis of volatile components of species", *Chromatographia*, 55, 729-735 (2002). DOI: <https://doi.org/10.1007/BF02491788>
2. D Cavanna, et al., "The scientific challenges in moving from targeted to non-targeted mass spectrometric methods for food fraud analysis", *Trends Food Sci Technol*, 80, 223-241 (2018). DOI: [10.1016/j.tifs.2018.08.007](https://doi.org/10.1016/j.tifs.2018.08.007)

Nitrogen – Whenever, Wherever

Gas generation presents a safer, more cost-effective, and more reliable alternative to traditional tanks – is it time you made the switch?

Most labs within the analytical field rely on a constant and/or reliable supply of gas. Traditionally, these gases are transported and stored in high-pressure cylinders – “gas tanks” – that increasingly feel like yesterday’s technology; they are unwieldy, inefficient, and fraught with issues that modern manufacturers should not need to accept. In-house gas generators offer a safer and cost-effective alternative to bulk gas supply, but how do you know if they are the right choice for your lab?

Here, Kelly Abernethy, Associate Director, Research and Development, Exela Pharma Services LLC, North Carolina, US, describes her experiences with PEAK Scientific’s nitrogen generation system.

Tell us a little about yourself and what you do...

I have been working in R&D at Exela Pharma Services for 12 years. Exela is a specialty pharmaceutical company that focuses on developing, manufacturing and marketing generic and proprietary sterile injectable products. As a pharmaceutical company, quality control is of paramount importance – and we conduct potency and impurity profiling for all of our products. Our analytical science capabilities, including mass spectrometry, are vital to the business.

How do you source gas supplies for your analytical science applications? Until around a month ago, we were using standard gas tanks. And, to be frank, we were struggling; for example,

a gas cylinder might run out in the middle of an analysis. Sometimes we’d need to order a replacement cylinder by special shipment to get it on time, adding unbudgeted costs. Furthermore, interruptions in the gas supply can damage analytical instrumentation. In other words, the instrument downtime associated with gas interruption is not only inconvenient, but also decreases operational efficiency. And that’s why we started looking for gas generators. We chose PEAK Scientific’s Solaris XE lab nitrogen generator for a number of reasons. Firstly, it is highly compatible with our existing instruments, such as the Waters equipment range. Secondly, it is competitively priced – always a big benefit to any lab. Thirdly, PEAK Scientific personnel are highly responsive. That latter point was extremely important to me when I was deciding which supplier to go for – if people can’t communicate in a timely manner when they are trying to sell you something, how slow will they be once you have actually bought

their product? Finally, we also consider the actual size of the unit; those who work in crowded laboratories are likely to appreciate the small footprint of the Solaris generator.

And what do the Solaris XE generators feed?

Our facility relies on two Solaris nitrogen generators hooked up to in-house air lines. One generator is set up with a Waters Acquity UPLC-MS system – the other with a Thermo Corona™ Veo™ RS charged aerosol detector (CAD).

How has switching to gas generation specifically helped your work?

When we relied on traditional gas tanks, we found that our activities could be constrained by cylinder stocks or gas suppliers. And that’s because most gas supply companies have scheduled deliveries; if we ran out of gas before delivery was due, we had to coordinate an emergency delivery – more complicated than it sounds. For example, we had to



Figure 1: The Solaris XE nitrogen generator

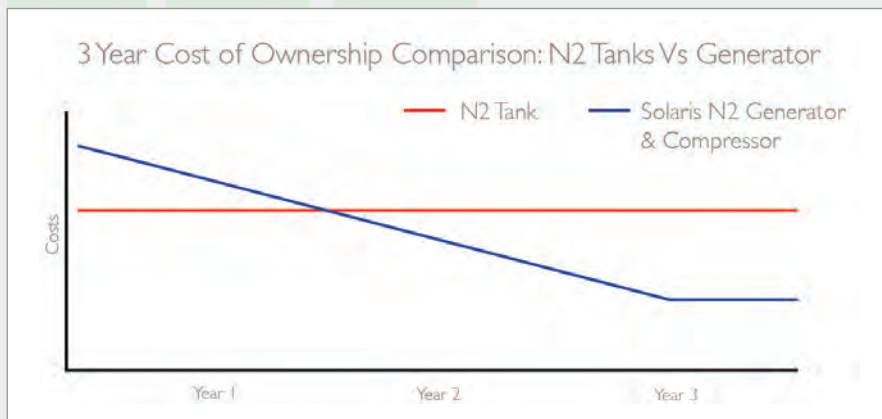


Figure 2: Cost comparison: nitrogen cylinders versus nitrogen generators

ensure that we got the correct tank, with appropriate high or low pressure regulators, for our specific instruments. But now that we have a gas generator, we don't need to time a study according to cylinder availability and delivery – we can do the work when it best suits us. We know the gas will always be there – and it's simply far more convenient. And it's safer: the gas tanks are heavy and awkward to move around – liquid nitrogen dewars are significantly larger than standard gas tanks, and require a special dolly for manipulation. There can also be safety risks associated with storing large volumes of gas at high pressure, so it's nice to dispense with those physical demands and potential sources of injury. In brief, the Solaris generator provides us with an uninterrupted supply of nitrogen, thereby optimizing the performance of our analytical instrumentation and avoiding the project delays associated with empty gas cylinders.

Was it simple to switch to the Solaris gas generator?

The purchase experience was excellent; we found the entire process to be smooth and rapid – all the way from requesting a code to turning on the machine. Also, the product arrived very promptly, which we appreciated. Importantly, the generators really are “plug-and-play.” Furthermore,

PEAK Scientific's post-purchase customer service has been excellent – and consistently thorough. Whenever we had a question, we received a very prompt response. Our service rep, Alison, even stopped by when she was in the area just to see how things were going – we are delighted with the product support we receive. And that echoes my original focus on choosing the right partner.

Does in-house gas generation have additional advantages in a pandemic?

Actually, yes. gas cylinder delivery people avoided entering customer premises to help reduce virus transmission – as per their company policies – and simply left tanks on the loading dock. And that meant we had to use our own time and personnel to retrieve the tanks and transport them to our containment facility. Now that we have an in-house gas generator, that drain on our staff resources – and the risk to health and safety – has been eliminated. In addition, of course, when there are fewer deliveries being made to our facilities, there is less chance of COVID-19 being brought to our site. Furthermore, there are environmental benefits – fewer deliveries means fewer road-miles and a reduced carbon cost. All in all, switching to in-house gas generation has a broad range of benefits, both direct and indirect.

The Solaris XE Nitrogen Generator

- Advanced system: membrane technology gas generation
- Broad range of applications: LC-MS, CAD, ELSD, sample preparation
- Flexible operation: flow rates up to 35 L/min; purity up to 99.5 percent; outlet pressure up to 116 psi
- User-friendly: LED colour indicators of instrument status
- Safe and convenient: avoids issues of pressurized cylinders, Dewars, or bulk storage
- Small footprint: compact chassis allows convenient, space-saving installation; can be placed on benchtop, mounted on wall, or stacked beneath other instrumentation weighing up to 100 kg (220 lbs)
- Cost-saving: compared with cylinders, gas generators provide 29 percent cost-savings over three years
- Peace of mind: 12 month on-site comprehensive warranty, backed by global on-premise servicing and technical support

EMPOWERING

the

ANALYTICAL

SCIENTIST

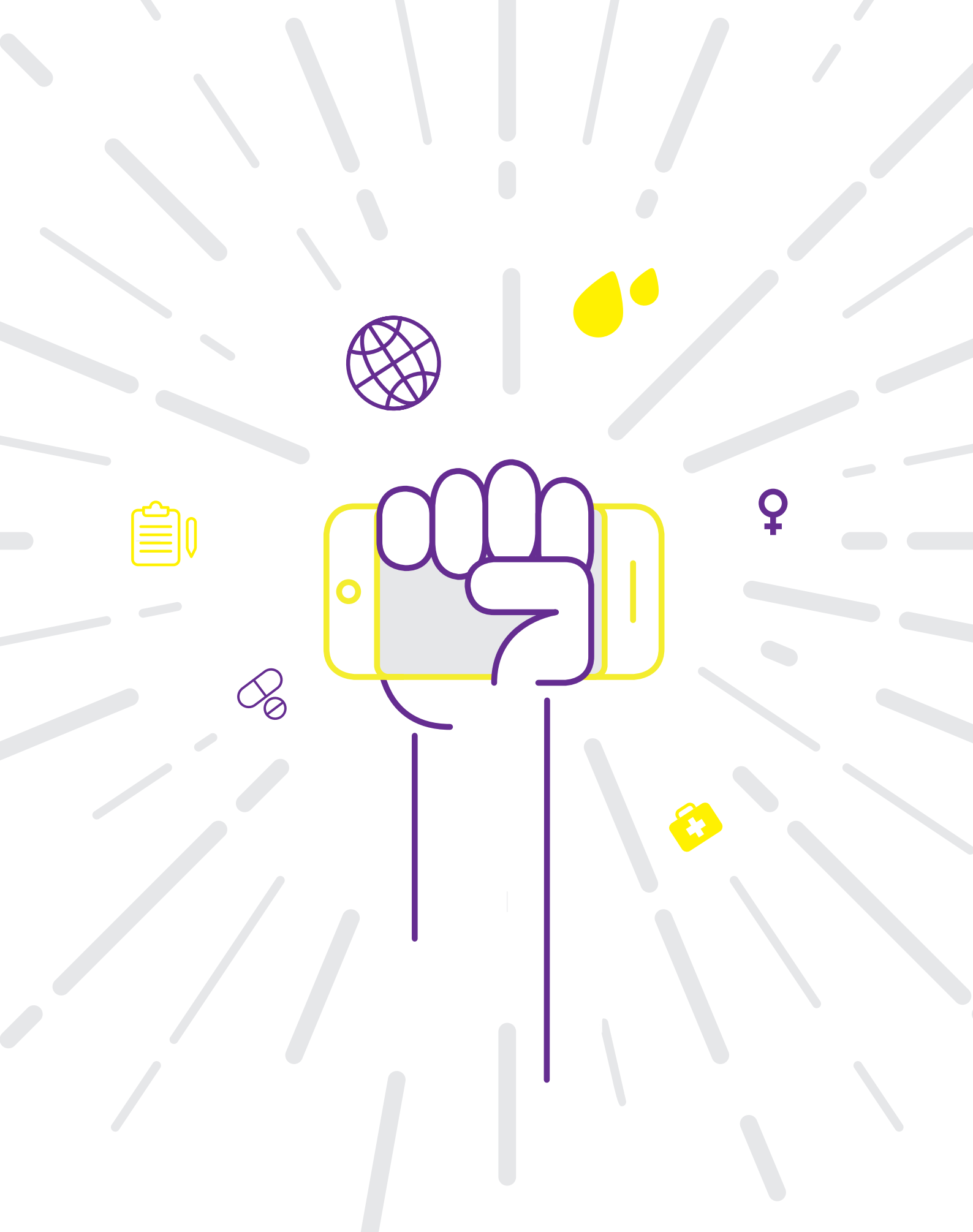
in

EVERYONE

Could the general public
prove to be key in the
next great phase of
analytical chemistry?

Say hello to citizen science!

*By Michel Nielen, FoodSmartphone
Coordinator and Principal Scientist
of Wageningen Food Safety Research
(WFSR) and Professor of Analytical
Chemistry at Wageningen University,
the Netherlands*



Citizen science represents a next logical step in the democratization of analytical chemistry. A central aspect of this endeavor is bringing the lab to the sample – or, put another way, taking measurements outside of the traditional lab environment.

At the forefront of this effort: designing simplified medical and analytical chemistry tools and making them accessible to citizens.

Of course, citizen science isn't a new concept. A classic example is the pregnancy test, which was developed and made available to the public around 50 years ago. And today's supermarket COVID-19 tests represent a similar development in response to the current pandemic. At our university, citizens have even supported a project studying the impact of climate change-driven disease migration on local insect populations by catching mosquito samples for analysis by experts in the lab.

All this stuff is great – but I can't help thinking there is so much more we can achieve with citizen science. In the case of COVID-19, for example, these tests should not provide a simple yes or no answer – they should communicate valuable data to stakeholders, such as those in government or industry. And, with modern smartphones, we could use location tracking and timestamping to add even more value with real-time geotemporal maps of the acquired data. Imagine the power of such a tool in the fight against the pandemic?

Beyond COVID-19, we could also employ a citizen science approach to fight other plagues of humanity, such as environmental pollution and food fraud. The possibilities are tantalizing and we're making progress, but where are we headed? How far have we gotten already? And what role does analytical chemistry play in this arena?

THE (ANALYTICAL) STATE OF AFFAIRS

Right now, many of analytical chemistry's contributions to citizen science exist in very simple forms. An example: pH testing of local surface waters – what could be simpler, right? But so many more tools are currently in development to form a bridge between analytical techniques and the public. Our FoodSmartphone project is a great example of a success story on this front (see Box 1: The Food Analyzer in Your Phone). This approach was simplified to the degree that even a teenager can perform a test without training.

In fact, we are very close to real-world implementation of citizen science devices in the area of food quality and safety. My colleague Yannick Weespoel has done some cutting-edge



THE FOOD ANALYZER IN YOUR PHONE

Michel Nielen answers our questions about the FoodSmartphone project

What's your mission with the FoodSmartphone project?

To bring the lab to the sample and rationalize the food quality and testing strategies in Europe. Current strategies rely on the classic (and limiting) dogma of sample acquisition in the field – on farms, at border inspection points, in supermarkets – and subsequent transport to labs. It can then take a day, a few days, a few weeks, or even a month to get results. Many of these samples are chosen at random, so we can waste lots of time analyzing the 99 percent of these that are destined to be safe and compliant. Clearly, this isn't totally effective! We thought: what if key stakeholders like farmers and food inspectors, and eventually citizens, could conduct the pre-screening themselves? And that's what we're aiming to facilitate!

Sounds great! And who's involved in the work?

The FoodSmartphone project was the result of a collaboration between seven leading institutes, including Wageningen Food Safety Research, Queen's University in Belfast, the Spanish National Research Council in Barcelona, the University of Chemistry and Technology in Prague, Linköping University in Sweden, CSEM in Switzerland, and Aquamarijn Microfiltration in the Netherlands. Then there were additional partner organizations from industry, like Barilla (Italy) and Zeulab (Spain), and academia too.

The project was divided into five different R&D packages. One such package focused on biorecognition;

one of our PhD students studied aptamers as alternatives to antibodies on this front, and others studied DNA-directed immobilization and antifouling. This all plays a pivotal role in the development of high-density, high-capacity biosensors. Then there were of course groups focusing on detection with the smartphone camera and smartphones used in combination with electrochemical devices.

And is the method looking promising?

The prototype 3D-printed surface-plasmon resonance (a label-free bio-interaction technique) biosensor on a smartphone is definitely a game changer – and it comes with a total cost of less than 100 euros. What's more, two different 3D-printed microfluidic sample preparation approaches have also emerged from our collaboration with the group at Linköping. Novel algorithms were defined for image recognition by the group in Belfast, too. As for the overall methodology, we previously developed a smartphone immuno-assay for a biomarkers in milk application with the Ozcan group (see the sidebar: Protecting our Environment – and our Patients!) in 2014. Back then it took around 90 minutes to finally obtain a result. Today, our fastest allergen test takes around 30 seconds.

Has the work attracted much attention?

Absolutely! Of course, we have great relationships with the companies that our institutes are collaborating with, and we've attracted massive publicity that is still ongoing! The FoodSmartphone project has been picked up by radio and television, national newspapers and all kinds of Internet sources. We were recently approached by a major food industry to discuss future collaboration opportunities on the phone project. This is, naturally, very exciting. Watch this space for updates!

PROTECTING OUR ENVIRONMENT — AND OUR PATIENTS!

A quick case study of citizen science in the fight for a healthy environment and optimal patient care in Lyme Disease

By Aydogan Ozcan, Professor, the University of California, Los Angeles (UCLA), and an HHMI Professor with the Howard Hughes Medical Institute

Identifying and characterizing microscopic objects in water is critical for many applications. Yet, traditional water monitoring technology relies on in-field sample collection with subsequent laboratory analysis by either manually operated microscopy or optics-based flow-cytometry devices, which are expensive and require expert resources.

Our group has developed innovative holographic imaging flow cytometer (IFC) prototypes for the rapid and automated identification and characterization of micro-objects in water. Our IFC device uses a lens-less image sensor to capture interference patterns caused by light passing through and around micro-objects in samples. Our system computes intensity and phase images for micro-objects in its field of view, which are processed to extract object features like size, color, morphology, aspect ratio, and thickness.

Our group has successfully applied this device to label-free monitoring of phytoplankton compositions and the identification of potentially harmful algae in ocean water, as well as pathogen identification (such as *Giardia* and *Cryptosporidium*) in drinking water. We are currently working with a company to commercialize this technology in a practical and cost-effective way. Our goal is to democratize high-performance

microscopic analysis and make it accessible for both professional and citizen users alike.

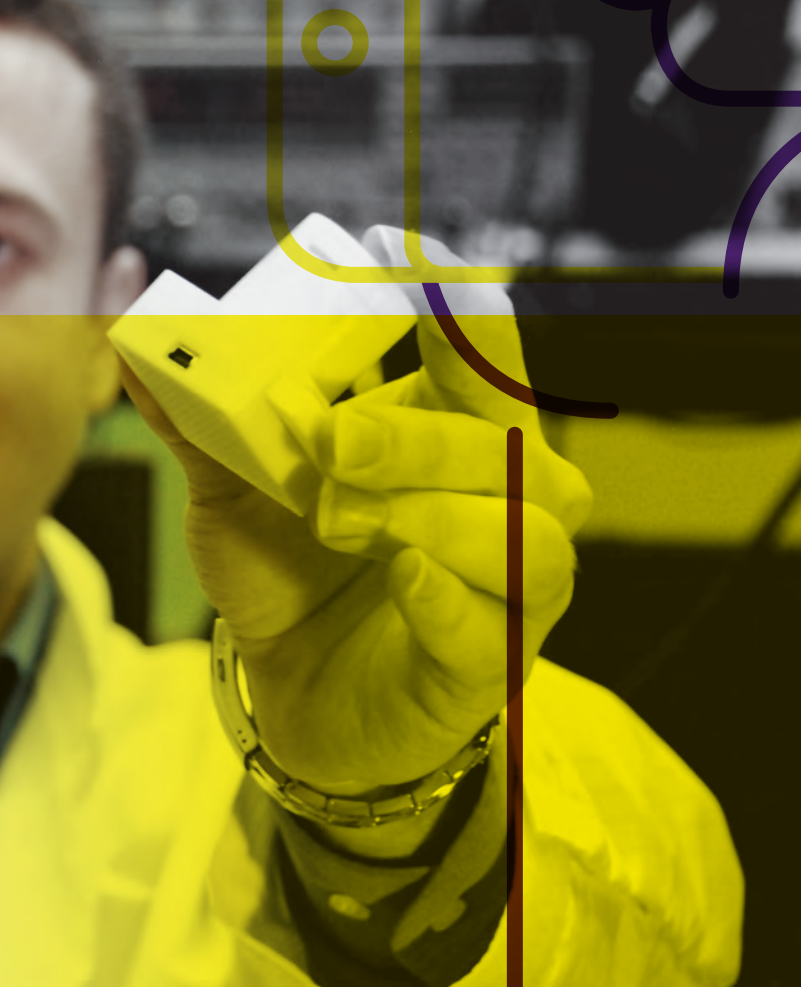
Citizen science accomplishes multiple goals at the same time. First, it allows participants to learn new skills and knowledge through direct experience. Second, the potential geographical spread of “citizen scientists” can allow us to tackle monitoring problems spread over large areas – and long periods of time, too. In these respects, environmental issues represent a rich set of problems for citizen scientists to address. Our work on phytoplankton compositions (which are sensitive to environmental changes and can lead to changes in water conditions that are dangerous for animals and people alike) is a great example of such an environmental application.

We have also explored the development of a multiplexed, paper-based sensor that harnesses mobile phones and deep learning to diagnose Lyme Disease via

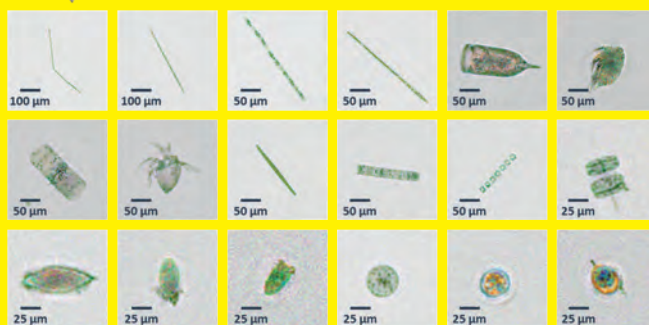
detection of a panel of target analytes. The current recommended approach – “two-tier serology” – has poor sensitivity for patients in the early stages of infection, in which antibiotic treatment is most effective. Our method takes only 15 minutes, is low cost, and can be conducted with a handheld mobile reader using a sandwich immunoassay!

Importantly, we also incorporated a synthetic peptide into our assay’s detection panel: modified-C6, composed of a C6-like epitope linked to a specific p41 epitope. This component of our assay elevates the diagnostic capability of our computational multiplexed vertical flow assay (xVFA), further increasing the reliability of our results. This xVFA was validated through a rigorous clinical study using samples from New York and Wisconsin. The result: 90.5 percent sensitivity and 87 percent specificity, which is – to our knowledge – the best diagnostic performance of a point-of-care test for Lyme Disease to date.





“ Though the devices are designed to be simple, the truth is that it takes a lot of work to bring analytical capabilities to the public. ”



The phytoplankton analyzer from Aydogan's group

work in the PlasmaFOOD EU-project and also collaborates with Jeroen Jansen's group (see the sidebar: Enabling Citizen Science). For example, by employing handheld, near-infrared scanners to determine the moisture, protein, and fat content of food products through their packaging at supermarkets. These are simple, low-cost devices that can communicate with smartphones and detect issues, such as adulteration or mislabeling. I imagine these handheld devices will have a bright future in such applications – maybe in as little as two years!

Though the devices are designed to be simple, the truth is that it takes a lot of work to bring analytical capabilities to the public. We are used to highly complex tools in academic and industrial lab environments, but simple tests with simple targets are needed when asking untrained individuals to play a role in research endeavors. A key part of this simplification is to identify single targets that can provide useful information about topics of interest. An example might be measuring a single metabolite that represents a metabolic pathway of interest in a disease versus measuring hundreds of related chemicals across the entire metabolome or microbiome.

“The answer moving forward is simplification – not only of the devices, but of the entire associated protocols, too.”

THE OBSTACLES AHEAD

We’re seeing the literature booming with portable devices and sensors, but – more often than not – when you delve a little deeper you discover that there’s, for example, a required incubation step of 60 to 90 minutes, the need for a sample preparation step that uses a high-speed centrifuge, or the use of very expensive materials. These are clear obstacles to adoption by true citizens. Long time windows can dissuade many from participation, and who has a spare centrifuge lying around the house?

The answer moving forward is simplification – not only of the devices, but of the entire associated protocols, too. We need these approaches to be foolproof, featuring quality-by-design principles that deal with the issues of false positive and false negative results. One effective way to achieve data reliability is to provide some sort of indication of the quality of the results to the user. When results are strong enough to use, these should be automatically communicated to databases or the people responsible for processing them. The inevitable risk of sampling errors will be at least partly compensated by the high numbers of data that become available.

A BRIGHTER FUTURE?

We aren’t quite where we would like to be yet. We have some great concepts, but there are problems and bottlenecks that

we must face before citizen science hits the mainstream. The required infrastructure is on its way, though! We should all be incredibly excited about this.

As for uptake of these endeavors by the public at large, we shall have to consider the social and psychological challenges as well. Not everyone will be interested in learning about and performing scientific tests. A direct personal benefit could change this, as would be the case with a specific health check, food quality check, or environmental exposure check. And we should also prepare for communication issues. Test results will inevitably be challenged on social media, as is the case with scientific information in general. A strong communication strategy will help us to inform users and tackle misinformation at its sources.

There is hope, though. The younger generation loves to play and fiddle with gadgets – I’d wager there’s a reasonable chance that they would also like to try their hand with analytical devices. People might be even more tempted by the process if it is associated with causes to which individuals have strong connections. Environmentalists, for example, might lead the way by going the extra mile in obtaining pollution samples for some of the large-scale studies in which citizen science will be a powerful weapon. On this example of pollutants, I would guess that it will take around four to five years for citizen contributions to make an appearance.

For some other applications like the handheld near infrared scanners, however, it might take as little as two years. Along the way we’ll need to traverse the dreaded development “valley of death” (in which significant financial input is needed to reach the other side). This will mean validating the methods in labs with experts, building field trials, producing devices at scale, and so on. Getting these instruments to members of the public will definitely take some yardage, but we are sure to reap the rewards when we do.

I for one look forward to the citizen-driven future of science!





ENABLING CITIZEN SCIENCE

Jeroen Jansen, Associate Professor, the Analytical Chemistry group at the Institute for Molecules and Materials, Radboud University, The Netherlands, discusses his forays in the world of citizen science

We lead the Citizen Science Innovation Initiative (CSII) – a joint effort between analytical departments of

several universities in the east of the Netherlands. Our ambition is to enable technology providers to reach a much-anticipated citizen science measurement solution alongside academic specialists. In that sense, the role of the citizen is – thus far – of limited importance. We want to change that.

As part of CSII, we worked with Nutricontrol to apply handheld near-infrared (NIR) sensors, which, for example, allow farmers to measure the quality of their animal feed in a reliable fashion. In another project, we used

handheld NIR to analyze the health and sustainability of chicken fillets through packaging in supermarkets. We have also developed breath analysis equipment to measure citizen health in any location with the Enose company. This tool could allow us to conduct such analyses outside hospitals, where most people are presumably quite healthy – but this may not always be the case!

Enabling citizens to conduct their own measurements is of the utmost importance. In the 21st century, citizens are learning to gather and use their data in innovative ways. Whether it be maintaining health, improving their living environment, or examining exactly what their family is eating, citizens want to know more than ever before. The latest technological developments mean that citizens no longer have to rely on institutions for such measurements.

The main challenge: most citizens are not analytical chemists... To be truly powerful, we need measurement technologies that can be used with relative ease. More importantly, these technologies need to be developed in such a way that everyone can trust the result, regardless of their level of expertise. These data may then contribute to a much broader repository of “global data” that empowers scientists.

Technologically, citizen science has great potential. Any analytical chemist, however, knows that every measurement has its limitations. Citizens who haven't received laboratory training may not understand these limitations. Turning all of these non-specialists into “*Homo metans*” (measuring humans!) is a big challenge. But this isn't just a social science challenge. Having anybody contribute to a large data repository with centralized chemometrics will require a large effort in calibration transfer, data matching from different devices, and data preprocessing to remove non-chemical perturbations.

Not To Be Missed: IMS-MS

Kevin Giles explores the wonderful world of IMS-MS, and Waters' key contributions to it

The power and flexibility of ion-mobility spectrometry-mass spectrometry (IMS-MS) enables accurate determination of a broad range of analytes – from small molecules to large protein complexes. The workflow and data quality advantages of IMS-MS instruments like the SELECT SERIES Cyclic IMS are increasingly driving the technology's use in both high-end research and towards more routine applications. Kevin Giles, Scientific Fellow, MS Research, Waters Corporation, UK, tells us more.



allowing nested acquisitions and high peak capacities. The upshot? Improved data quality and enhanced confidence in results. Furthermore, as IMS sits after sample ionization, the method is particularly valuable for ambient ionization approaches (such as DESI, ASAP or REIMS), MALDI and MS imaging, where upstream chromatography is not possible. Finally, IMS can determine gas-phase collision cross-section (CCS) values of ionized analytes. That's important because CCS values relate to gas-phase structures and can be used to identify species (through comparison with theoretically-derived CCS values) and as an additional confirmation metric in screening experiments (using CCS libraries). For all these reasons, we are seeing increasing interest in IMS-MS.

How have you responded to this increased interest?

Our recent webinar series (see the sidebar "IMS-MS Webinar Series") answers many common questions and requests for advice. For example, the "Introduction to Ion Mobility and the SELECT SERIES Cyclic IMS" presentation outlines the basic principles of ion mobility separation and the unique capabilities of the Cyclic IMS-MS system.

Why was the Cyclic IMS-MS developed? In short, it's the natural result of Waters' constant drive to improve performance characteristics and functionality of our analytical technologies. The Cyclic IMS-MS system advantages include increased IM separation capability, multi-functional operating modes (providing more in-depth molecular characterization) seamlessly integrated in an enhanced Q-ToF MS with m/z resolution up to 100,000, mass accuracy down to 500 ppb, increased sensitivity (especially for more labile species), and improved dynamic range. Given all the advantages, I suppose the question should be, "Why would you not develop such an IMS-MS system?"

And what makes the Cyclic IMS instrument unique?

Like Waters' SYNAPT instruments, it has a Q-IM-ToF geometry (all other manufacturers use an IM-Q-ToF geometry). Crucially, these instruments feature collision cell placement before IM separation, as well as after, which permits separation of fragment ions from m/z -selected precursors and measurement of CCS values to aid structural determination. Importantly, the cyclic IMS allows multi-pass operation, providing user-selectable resolving power, which we've shown to scale from ~65 (for one pass) to >750 (for 100 passes). Such performance is unmatched in a commercial instrument. But perhaps the most unique feature of the Cyclic IMS is its ability to perform IMSⁿ acquisitions, analogous to the MSⁿ mode in ion traps, which allows structural analysis of unparalleled detail. And users get all these features in a remarkably small footprint!

What main challenges were encountered during development of the Cyclic IMS?

There were a number of challenges in the development of the Cyclic IMS device. One critical issue we faced was related to control of ions at the interface between

IMS-MS Webinar Series – View on demand

- Kevin Giles, Waters Corporation - Ion Mobility and the SELECT SERIES Cyclic IMS
- David Ropartz, INRAE - Characterization of oligo-/ polysaccharides
- Joseph Zaia, Boston University - Characterization of glycopeptides
- Libin Xu, University of Washington - Lipid Profiling and MS Imaging
- Ralf Laux, Boehringer Ingelheim and Ian Wilson, Imperial College London - MetID and structural elucidation
- Mark Skehel, MRC LMB Cambridge - HDX/MS Experiments

IMS-MS Webinar 1

Q&A highlights

Expert panel: Dale Cooper-Shepherd and Kevin Giles

Can Cyclic IMS both separate structural conformers and also isolate/trap them for further investigation?

KG: Yes. The unique geometry of this system permits selection of sub-populations of mobility-separated ions, followed by their activation and reintroduction into the instrument for further mobility separation. We can repeat this sequence in an IMSⁿ experimental design that is analogous to MSⁿ.

What is the duty cycle efficiency of Cyclic IMS?

KG: A crucial feature of our mobility systems is that, while the instruments are performing one mobility separation, they are also accumulating the set of ions for the next mobility separation. And that's why our duty cycle is close to 100 percent.

What is the role of the step-wave?

KG: It efficiently transfers ions from the source to the mass analyzer. Note that ions are focused off-axis, then transferred to the mass analyzer through differential apertures. The off-axis design moves ions orthogonally to the main flow of the gas – and that helps keep the system clean; any droplets from the ion source simply pass straight through.

What are the main benefits of IMS?

D C-S: When interrogating complex samples, some analytes (including isomers) may co-elute; separation by ion mobility allows us to discriminate between these species. Also, IMS supports measurement of collision cross section (CCS), which can be compared with a CCS library, giving extra confidence in analyte identification – especially for very low-level species.

What fragmentation options are compatible with Cyclic IMS?

D C-S: The standard fragmentation method is collision-induced dissociation, which we can do either before or after the ion mobility step. In IMSⁿ experiments, dissociation can be effected within the

Cyclic device between rounds of ion mobility. Last year, we introduced electron capture dissociation – a complementary fragmentation technique frequently applied to protein and peptide studies; again, this can be used before or after ion mobility. Also, we recently implemented surface-induced dissociation (SID), which allows us to dissect the interconnectivity of non-covalent interactions within native protein complexes.

Are multiple pass separation times compatible with LC?

KG: Yes. Typical separations of 2-5 passes take less than 100 milliseconds. And even if you opt for the extreme, say 100 passes, it needs only ~1.5 seconds.

Do prolonged times in the ion mobility region adversely affect resolution?

KG: No. Although ions spend longer in the device, they cannot significantly diffuse radially because they are confined; at the same time though, they are being separated axially – and this step obviously improves the resolving power of the system as increasingly longer drift paths, hence residence times, are used.

the main ion optical axis of the instrument and the orthogonal Cyclic IMS device. To address this, we created an electrode array in which ion movement could be changed by switching the direction of the traveling waves used for ion propulsion and mobility separation. This system facilitates ion entry/exit from the Cyclic IMS, including mobility-selected ejection used in IMSⁿ.

Are there any unsung heroes in the development of the Cyclic IMS?

Bringing a product to market involves many people, and the Cyclic IMS instrument is a testament to the skill and creativity of the entire Waters team in Wilmslow, UK. But I would like to give particular mention to Peter Carney, Bharat Chande, John Garside, Paul McIver, and Peter Nixon, who were pivotal in developing the first Cyclic IMS prototype back in 2014.

What research has Cyclic IMS facilitated?

Some early work we did with David Ropartz at INRAE provides a particularly interesting example. We used the Cyclic IMS to separate isomeric reducing pentasaccharides; by combining this approach with higher resolution analysis, IMSⁿ and isotope labeling, we confirmed mobility separation of the anomeric forms. The application of IMSⁿ to locate structural modifications in isomeric species is potentially very far-reaching!

What customer feedback have you received?

All very positive! By participating in the Cyclic IMS community, we can see that analysts' imaginations have been captured by the flexibility of Cyclic IMS operation, both in terms of "dial-up" resolution and IMSⁿ capability. They

also very much appreciate the raw performance power of the instrument. Frequently, this translates into the best feedback of all – a decision to purchase a SELECT SERIES Cyclic IMS instrument. People only buy instruments if they believe in their value!

What is the future of IMS-MS?

I think there is a very bright future, both in its growing use as a routine analytical tool, enhancing workflows and data quality, and as a powerful research tool to help unravel some of the most complex analytical challenges. Overall, it will play a central role in progressing our customers' science across a wide range of application areas.



The Return of CannaQAP

Melissa Phillips tells us about NIST's mission to improve cannabis testing

As the US National Institute for Standards and Technology (NIST) rolls out the second exercise in its cannabis quality assurance program (CannaQAP), the spotlight is on dried flower – with an emphasis on distinguishing hemp from “drug-type” cannabis. We caught up with NIST Research Chemist Melissa Phillips to find out more.

What's the goal of CannaQAP? CannaQAP will provide interlaboratory studies twice a year to the cannabis testing community (including product developers, forensics labs, third-party testing labs, and regulators). Our QAPs are designed to assist laboratories in demonstrating and improving measurement comparability and/or competence in challenging or emerging

areas. Laboratories participating in CannaQAP benefit from an objective evaluation of their analytical approach through comparison of their results to other participants and to data provided by NIST.

What response have you had from labs? The response has been overwhelmingly positive! The number of participants is exceptional (over 100 labs requested samples for Exercise 1 and 80 percent returned results), and we've had lots of feedback thanking us for developing this program and for our commitment to helping the community improve.

In Exercise 1, which focused on the determination of cannabinoids in hemp oils, almost two-thirds of our participants were contract testing

Solutions

*Real analytical problems
Collaborative expertise
Novel applications*





View From the Cannabis Lab

Amber Wise, Scientific Director at Washington-based Medicine Creek Analytics, tells us about the lab's experience with CannaQAP

We decided to take part in CannaQAP because we feel it's important to increase the amount of data we have regarding cannabis in all areas, and we want to contribute to moving the science forward at every opportunity. Every state that has a legal cannabis program has their own rules, which also applies to testing requirements, so we felt having a comparison of what labs

are doing all across the USA would be useful to gauge our performance.

We signed up for Exercise 1 and found it very straightforward—we just processed the samples like any other client sample. The preliminary data we have been sent indicate we were very close to the mean and average, which is a good sign.

We have now signed up for Exercise 2, and we're particularly interested in the metals testing aspect. We test for an expanded list of metals but we still don't cover all the ones on the NIST list, and not many labs test for metals beyond arsenic, lead, mercury, and cadmium.

I would absolutely encourage other labs to take part—it's similar to a proficiency test but with fewer consequences. Just process the sample like normal and enter the values in the database—easy! There's really no reason not to participate

“Laboratories participating in CannaQAP benefit from an objective evaluation of their analytical approach through comparison of their results to other participants and to data provided by NIST.”

laboratories, and about 10 percent were product developers. For Exercise 2, we anticipate that we will see a greater proportion of forensic labs.

Can you share any results from the first exercise?

We provided the preliminary results to participants in December, allowing them an opportunity to review and correct any errors. The final report is in preparation, and we hope to publish it in the next couple of months.

What will the second exercise involve? Participants in Exercise 2 will measure cannabinoids, moisture, and/or toxic elements in cannabis plant samples, which will introduce another level of

difficulty for participants compared with Exercise 1, as most laboratories will need to extract or isolate the cannabinoids from the plant materials (not required for analysis of hemp oils). As legislation on hemp refers to THC levels on a “dry-weight basis,” we are also including an opportunity for laboratories to report the measured moisture in the plant samples for comparison to NIST and the community.

Toxic elements (arsenic, cadmium, lead, mercury, and more) that can contaminate cannabis plants based on the growing conditions (soil, water, fertilizers) and processing approach (grinding) will also be a focus of Exercise 2. In addition to hemp

samples, a second set of marijuana samples (THC > 0.3 percent) will be available to laboratories that can demonstrate appropriate DEA licensing and/or foreign import permits. These additional samples will contain THC greater than the amount permitted in hemp, to allow laboratories to evaluate their methods with samples that would normally fail a QC check.

Why should labs consider signing up? Signing up for CannaQAP allows laboratories to evaluate and improve their own operations, simultaneously helping the overall cannabis community increase confidence in laboratory measurements. The program operates very similarly to a proficiency testing scheme but without the judgment and related corrective actions of a pass/fail grade. All results from CannaQAP will be peer-reviewed and made publicly available as published NIST Internal Reports. The results will



be anonymized so that readers can see the amount of variation between labs but not how any specific lab performed (participants will know their own performance, of course). An added bonus is that remainder samples from CannaQAP studies can be retained by participants and used for quality control in the future, while NIST works to develop reference materials.

What makes NIST so well-placed to run such a program?

NIST's long history of work in the areas of foods, dietary supplements, tobacco, and other natural products has primed us for work on cannabis, despite its unique legal and analytical challenges. We are experts in analytical chemistry as applied to these types of

products and have the know-how to anticipate and remedy any challenges in extraction, stability, homogeneity, and instrumental analysis that might arise. We are also fortunate to have colleagues and collaborators such as the National Research Council of Canada that we can reach out to for additional information and troubleshooting if necessary, and a community of cannabis testing laboratories supporting our efforts who are extremely willing to share insights and experience and assist us in our mission in any way that they can.

What other cannabis-related projects does NIST have in the pipeline?

In addition to helping labs demonstrate and improve their measurement

capabilities, CannaQAP is assisting us in the design and characterization of cannabis reference materials. NIST is currently working on the development of a hemp plant reference material, which we hope to release in early 2022. NIST is also developing numerous analytical methods based on various technologies (including LC-MS, GC-MS/MS, and spectroscopy techniques) that can be directly transferred to forensic or industry laboratories.

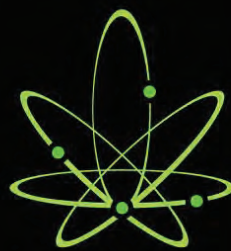
One group at NIST is working to develop an objective colorimetric test that will allow greater confidence in the quantitation claims of screening approaches, and another group is doing fundamental research toward the development of an accurate marijuana breathalyzer.

RESTEK | ADVANTAGE

See What It Can Do for You and Your Lab



Sign up today to access Restek's years of chromatography knowledge at www.restek.com/advantage



CANNABIS
SCIENCE
CONFERENCE

LIVE, IN-PERSON SHOW!
CANNA BOOT CAMP
EXCITING KEYNOTES
HUGE EXHIBITION FLOOR
CULTIVATION GURUS
ANALYTICAL EXPERTS
MEDICAL EXPERTS
NETWORKING MIXERS

BALTIMORE, MD
September 13-15, 2021

BALTIMORE CONVENTION CENTER

*The World's Largest Scientific
& Medical Cannabis Event!*



SAVE THE DATE
for our
West Coast Event!

LONG BEACH, CA
February 2 - 4, 2022



LONG BEACH
Convention & Entertainment Center

Sponsorship and exhibition opportunities are available.
Please contact Andrea at Andrea@CannabisScienceConference.com

CannabisScienceConference.com

Quantification of Phthalates in CE & RoHS Compliance Testing

The requirements for a CE mark now include the requirements for RoHS compliance, which consists of the disclosure of 4 phthalates: Bis(2-Ethylhexyl) phthalate (DEHP), Benzyl butyl phthalate (BBP), di-n-butyl phthalate (DBP), Diisobutyl phthalate (DIBP). A quantification method is defined in IEC 62321- 8 by a TD (Thermal Desorption)-GC-MS technique. The CDS 6150 Pyroprobe

is a multi-function thermal sample injection system for GC-MS, meeting and exceeding the RoHS phthalates testing requirements.

Table 1 shows the RSD (n=8) averaged at 3.2 percent, 3 times better than the method requirement, with MDLs all below 25 ppm, 4 times better than the method requirement.

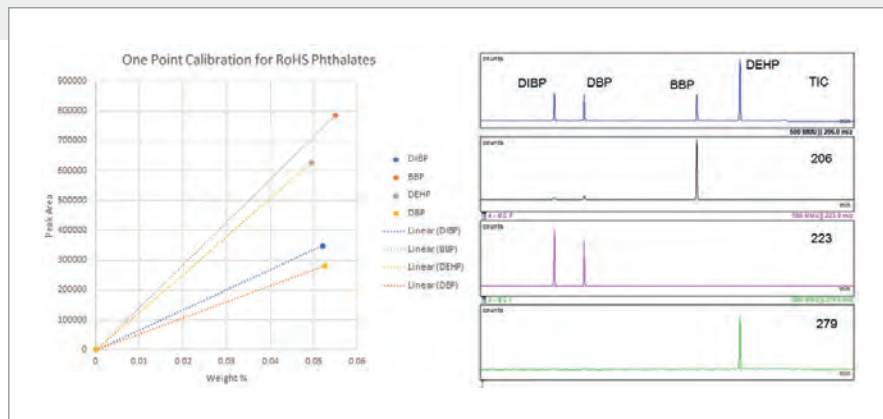


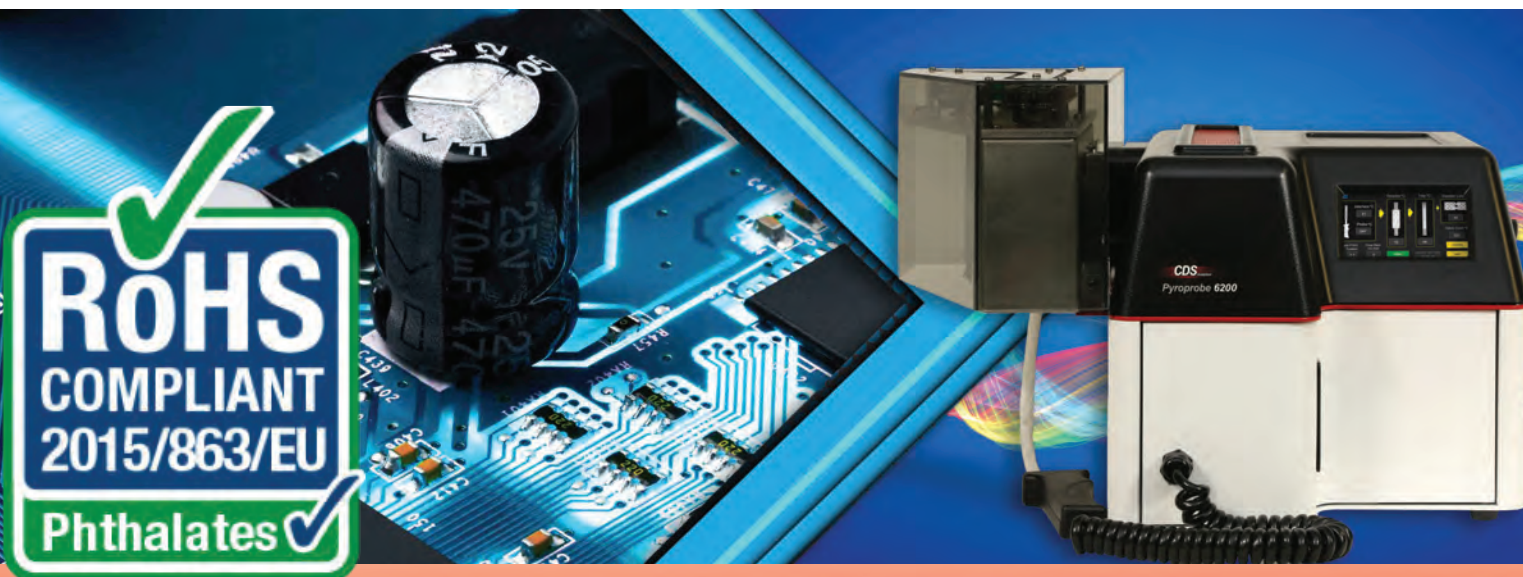
Figure 1: Single point calibration and chromatograms (TIC and EICs) for the four phthalates.

Phthalate	Area RSD	MDL
DIBP	3.2%	21.7ppm
DBP	2.3%	21.0ppm
BBP	4.3%	21.0ppm
DEHP	2.9%	14.7ppm

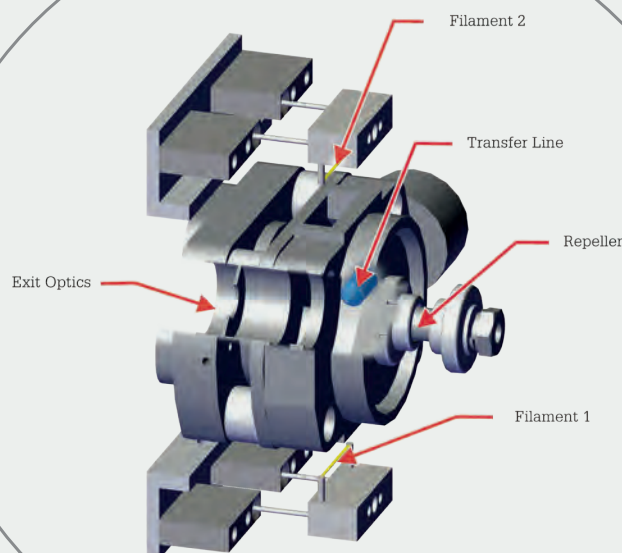
Figure 2: Single point calibration and chromatograms (TIC and EICs) for the four phthalates.

Multi-functional Thermal Injection System

Add Evolved Gas Analysis, Thermal Desorption, Flash Pyrolysis, Photochemistry, Thermal Slicing, Dynamic Headspace, SPME, Kinetics and Fixed Gas Analysis Techniques to Your GC-MS System



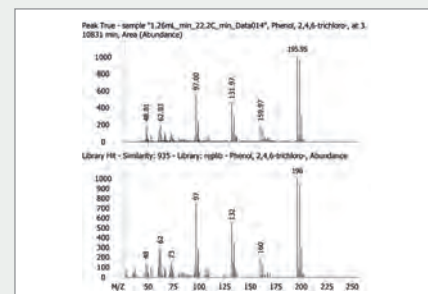
Spotlight on... Technology



Turn to Fast GC & Hydrogen Carrier Gas with Confidence

Transfer your applications to Fast GC using Hydrogen seamlessly! LECO's Pegasus® BT GC-TOF-MS has a uniquely open designed StayClean® ion source which never needs cleaning. You can speed up your analyses using hydrogen, without sacrificing the sensitivity & spectral quality you need, ensure your MS library matching and rely upon incredible, fast acquisition, full mass range, data robustness.

Read more at
<https://info.leco.com/fast-gc>





timsTOF SCP

The timsTOF SCP for quantitative single cell biology research with unbiased, deep single-cell 4D-Proteomics™, immuno-peptidomics, epiproteomics and PTM analysis to complement scRNA-seq. Expanding the horizons of single cell research

Read more at <https://bit.ly/2REQWWa>



timsTOF Pro 2

The timsTOF Pro 2, powered by the latest parallel accumulation serial fragmentation (PASEF®) technology, paves the way to 4D-Proteomics and 4D-Lipidomics with unbiased cell and plasma proteomics and liquid biopsy multiomic biomarker discovery, integrating genomics with proteomics and epiproteomics.

Read more at <https://bit.ly/3wd9NXg>



Superior, Repeatable, Traceable Pipetting with the Andrew+ Pipetting Robot

Andrew+ offers fully automated pipetting executed using OneLab software, as well as more complex manipulations, using a wide range of Domino Accessories. OneLab makes compliance to requirements easy, as required by FDA 21 CFR Part 11 and EU Annex 11, enabling regulated labs to take care of documentation requirements, without compromising its market leading versatility and ease of use.

For demo register: <https://bit.ly/35vNznZ>



WITec alpha300 apyrion – Fully Automated Raman Imaging Microscope

The WITec alpha300 apyrion can self-align and self-calibrate for speed and consistency while also substantially reducing the researcher's experimental workload, enhancing reproducibility and eliminating potential sources of error. Its motorized components offer new optical capabilities, enhanced configurability and remote operation, even from home.

<https://www.witec.de/products/raman-microscopes/apyrion-automated-raman-imaging/>



HIAC 9703+ Pharmaceutical Particle Counter

The HIAC 9703+ liquid particle counters are the leader in Pharmaceutical USP <788> quality control and research applications. Designed for your liquid particle counting application needs, the HIAC 9703+ is highly configurable and easy to use. PharmSpec software makes data management easy and assures security for 21 CFR Part 11 environments.

Read more at <https://bit.ly/3ek7QRq>



Vi-CELL BLU Cell Viability Analyzer by Beckman Coulter Life Sciences

The Vi-CELL BLU automates the widely accepted trypan blue dye exclusion method for cell viability. This makes it perfect for large to small scale cell viability/counting applications in many fields including biopharma and academia: Log-in samples on the fly, single sign-on with Active Directory, small sample volume requirements, strong instrument-to-instrument comparability.

Read more at <https://bit.ly/3nm3opr>

A portrait of Michel Nielen, a man with white hair and glasses, smiling. He is wearing a blue blazer over a light blue striped shirt and an orange lanyard. The background is dark with some horizontal light strips. There are diagonal blue and grey overlays on the image.

A Selective Food Directive

Sitting Down With... Michel Nielen, Principal Scientist of Wageningen Food Safety Research (WFSR) and Professor of Analytical Chemistry at Wageningen University, Wageningen, the Netherlands

Please tell us about your current position. I'm currently professor of analytical chemistry at Wageningen University, and I'm also the principal scientist at the applied research institute Wageningen Food Safety Research (WFSR). As principal scientist, I'm responsible for the strategy of the R&D program – so I am involved in things like chairing our research committee, coaching talent and advising the board on strategic R&D decisions. It's a multidisciplinary institute, so our activities range from analytical chemistry to toxicology, microbiology, and data science. In addition to these roles, I am also coordinator of the European MSCA ITN project FoodSmartphone and co-chair of the Recent Advances in Food Analysis (RAFA) symposium series.

What are some of the highlights from your career in analytical chemistry?

I have a long history in analytical chemistry. I started out four decades ago doing my master's research at Leiden University. At the time, we were developing low-dispersion post-column reactors for HPLC – this was before LC-MS was invented of course – and the idea was to address some of the selectivity challenges with current HPLC-UV methods by performing chemical reactions after the column. Alas, these reactors had issues of their own. We ended up solving a lot of them by developing segmented-flow reactors that enabled longer reaction times and, eventually, even performed on-line immunoassay detection after HPLC for the first time. That was a highlight of my early career that has influenced my later research, combining instrumental analysis with biorecognition assays.

After my master's, I did my PhD at the Free University of Amsterdam, where I became interested in bringing additional selectivity to HPLC-UV via on-line SPE. I then spent 10 years in

industry at AkzoNobel. That was an amazing period in my career, because I spent a lot of time exploring novel technologies. I managed to convince them to get one of the first API-MS systems, because we were encountering a lot of impurities – thanks to the separation power of the new technique CZE – and struggled to identify them. This turned out to be quite an achievement; we ended up proving that electrospray ionization could be used for not only small molecules and proteins, but also synthetic polymers. Later on, we combined this with MALDI MS and ended up producing one of the most widely cited review papers on the subject. After my time in industry, I came almost full circle in my career by returning to academia. Now, once more, my focus is on selectivity in analytical chemistry.

You refer to “selectivity” as a common thread throughout your career. Can you tell us more?

To me, there are three fundamental questions in analytical chemistry: What's in there? How much is in there? And where exactly is it located? That first question is essentially the issue of selectivity and it's something I've focused on in many different ways. To illustrate what I mean, I'll use an example from my time as an expert witness in a specific court case for the government. Once, the judge asked how I could be sure that there was no other molecule on the planet that would yield a similar LC-MS signature to the banned substance under investigation. I'd never thought about it like that. Until that point, we'd followed the official EU legislation – determining retention time, checking against reference standards, determining the relative abundances of certain ions, and checking that they didn't deviate too much. So this really got me thinking.

In the years following that case, one of my PhD students worked on a way to give a quantitative measurement of the selectivity of an LC-MS result. He derived empirical relationships between all kinds of molecules in databases across the globe and came up with a probability function that we could apply and tell the court, essentially, how (un)likely it was that another molecule could mimic the result given as evidence. This nicely illustrates what we mean by selectivity.

What keeps you awake at night?

Mainly rather crazy ideas and concepts, but in the past court cases kept me awake because they were stressful situations. More generally, I don't like how scientists' integrity is often called into question. Your position as an expert witness is obviously independent in a court case but, quite often, it turns into a debate about the expert's own integrity and that of their institution. It's something I don't like to see happen.

What is your key message to analytical scientists nowadays?

We need to learn how to improve our communication with target audiences. People should be aware – whether the audience is a group of scientists, marketers, industry people, or the general public – of how to correctly communicate the work they are doing. One of the key things we should be looking to develop in young scientists is the ability to deal with the doubts around lab testing. It's not only an issue in court cases; in general society, we see that governments and scientists are being trusted less and less. As analytical scientists, we cannot ignore that situation and we certainly have a role to play in remedying it. From my perspective, it would be beneficial to build aspects such as social science, psychology, and marketing techniques into our analytical education.



See What You've Been Missing

What you see depends on how you're looking at it. Are you sure you're seeing your whole sample? LECO's Pegasus® BT is the world's most sensitive full-scan mass spectrometer, while the Pegasus HRT⁺ adds industry-leading mass accuracy to its high performance analyses.

- *The power of GCxGC allows you to see more in every sample*
- *Accurate mass and Identification Grading System (IGS) allows easy identification of "known-unknowns"*
- *Unrivalled full-scan sensitivity*
- *Lab-validated and -tested reliability and durability*

With just one run, see all the intricacies of your metabolomic samples. You'll have the answers at your fingertips, even when the questions change.

Learn More: <https://info.leco.com/see-whats-missing>



info@leco.com
www.leco.com | © 2020 LECO Corporation

LECO
EMPOWERING RESULTS