the Cannabis Scientist

SPECIAL SERIES:

Keeping Cannabis Consumers Safe

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IN MY VIEW

Heavy Metal Measurement Made Light

Heavy metal contaminants pose a risk to health – the cannabis industry must react accordingly.

The legal, cultural, and societal acceptance of cannabis as a therapeutic or recreational drug has exploded in recent years. Concurrently, concern regarding the presence of contaminants – notably pesticides, residual solvents, mycotoxins, and heavy metals – in commercial cannabis products has increased. Heavy metals can interfere with metabolic functions by mimicking metals that are vital enzyme components, ultimately inhibiting their normal function. The result of chronic heavy metal ingestion is damage to a variety of vital organs, including nervous system and kidneys. Moreover, heavy metals can be mutagenic, causing damage to DNA, and leading to a cascade of further problems such as tumor growth.

For cannabis, standards organizations, such as ASTM International, are in the process of developing consensus methods for assessing contaminants, including heavy metals, in cannabis. We should expect the number of metals covered by such methods and regulations will only continue to grow and target concentration levels will continue to decline. The metals of immediate concern have been arsenic, cadmium, lead, and mercury; however, in some jurisdictions, this has expanded to include others, such as barium, chromium, selenium, and silver. The nonuniformity of regulations between states and between countries has proven to be a particular challenge. In the US, these challenges will continue until there are federal guidelines akin to those for pharmaceuticals (FDA) or food products (USDA). The cannabis testing industry will likely contribute to the basis for the inevitable federal guidelines through participation and contribution to voluntary consensus standards development through organizations such as ASTM International and AOAC International.

Most laboratories assess the metal composition of cannabis products by digesting samples in an acidic matrix and conducting analysis with inductively coupled plasma mass spectrometry (ICP-MS). This technique has high sensitivity – in the parts per trillion range for most elements. ICP-MS also affords the advantage of rapid sample throughput, with typical analysis times of around 2–3 minutes per sample. Advances in instrument hardware and software have also made modern ICP-MS instruments much more user-friendly than their predecessors, meaning they can be operated by a much wider panel of users than previously possible.

"As legalization efforts continue, the methods for detecting metals and other contaminants will likely include a greater number of target compounds at increasingly stringent detection limits."

Testing currently focuses on the end product to be supplied, whether that be cannabis flower, extracts (waxes or oils, for example), or cannabis edibles. However, it is possible that testing will expand to include sources of contamination outside the product itself. Several recent studies have demonstrated the sputtering and vaporization of heavy metals from heating filaments in vaporizers and so-called "vape-pens" (1). In this case, the cannabis product itself is free from metal contamination, but the user exposes themselves to metals by using the vaporizer; this scenario is analogous to drinking clean water delivered to the tap by lead-contaminated plumbing.

Metal analysis will form a necessary component of more comprehensive testing of cannabis product purity and safety. As legalization efforts continue, the methods for detecting metals and other contaminants will likely include a greater number of target compounds at increasingly stringent detection limits. Nevertheless, as methods become increasingly harmonized between states, countries, and standards organizations, the challenges the cannabis industry faces should narrow.

To tackle the myriad challenges with metals testing in cannabis, it behooves the industry, including testing laboratories, instrument vendors, and regulatory agencies to understand the issues of metals contamination and to unify on validated methods for sampling, sample preparation, and sample analysis. Some of this work is being done and exchanged at conferences and symposia focused on cannabis, which are excellent venues to share the growing body of knowledge. Additionally, committees within ASTM International are beginning to codify standard test methods, which will likely form a framework for future federal regulation. It is incumbent upon the entire industry to advance our scientific understanding of cannabis as its chemistry, various uses, and legitimacy continue to grow.

Andrew Fornadel, Marketing Manager, Shimadzu Scientific Instruments, Columbia, Maryland, USA
Bob Clifford, General Manager of Marketing, Shimadzu Scientific Instruments, Columbia, Maryland, USA.

REFERENCES AVAILABLE ONLINE

IN MY VIEW

Taking Back Cannabis Control

Ill-considered regulations have resulted in an analytical race to the bottom. If you aim for best rather than worst, you have a part to play in shaping the future of our cannabis-testing field.

Over the last few years, cannabis testing has seen serious change – and it has become a very "interesting" business. Years ago, when there were no regulations, some labs were bringing the best science possible to the table so that we could help provide the industry with the information it needed to move onwards and upwards. But as more stringent regulations have come online, what we've witnessed is akin to the top blowing off a pressure cooker.

The regulators entered the game with their own views and ideas. They didn't pay a great deal of attention to the existing testing landscape; in truth, they were somewhat ignorant to the groundwork already laid out – and there was very little discussion with the labs that had helped establish testing in the industry; for example, Steep Hill, SC Labs, and CW Analytical Laboratories. And so, we were suddenly subjected to regulations that appear to have been constructed in a vacuum – or at least without a lot of forethought. Imagine laying out regulatory framework for an industry without performing in-house checks to ensure suitability – or even possibility…

Well, when the Californian regulations hit, the state didn't have its own reference laboratory. The scuttlebutt? As the scientists at California's Bureau of Cannabis Control (BCC) attempt to meet the same regulations handed down to us, those regulations are starting to change. Go figure!

Terpenes, for example, are extremely labile – they are volatile organic compounds, after all; in most other industries, recovery acceptance criteria for a standard in a batch run would be ± 30–40 percent. The BCC wanted ± 20 percent – almost impossible for most of the compounds. It was later changed to ± 30 percent, when the BCC acknowledged the issue, and some compounds like volatile monoterpenes are still difficult to get within the ± 30 percent acceptance criteria. And this is not an isolated example.

Some of those wayward regulations have been modified, but there are still others that make no sense. The microbial testing regulations are one example. Consider Aspergillus, E. coli or salmonella – the acceptance criteria state: "not detected in one gram." But what on God's green earth does that mean? Not detected by what methodology and on what measurement scale? There is no other regulated testing space where an action threshold is defined as "not detected in 1 gram", this is akin to trying to prove a negative.

"The industry has been sent down a 'lab shopping' pathway, where some growers seek those labs with the worst equipment for pesticides and the least sensitive microbial tests!"

For pesticides, some regulations state that your instrumentation must be capable of attaining a limit of quantitation (LOQ) of at least 100 ppb. But here's the crazy part: if you can meet that LOQ, you have to fail product on any level detected – whatever the limit of detection (LOD) of your analytical setup. At the LOQ, where you've got a signal-to-noise ratio of 10 to 1, everything is hunky-dory – the calls you make are the correct calls. But at the LOD, which means you are barely above the "noise" or background, hence the word 'limit', you're working at a ragged edge that produces false positives and false negatives at a fairly significant rate by definition.

With such ambiguous or ill-defined regulations, there is a dire consequence. The industry has been sent down a "lab shopping" pathway, where some growers seek those labs with the worst equipment for pesticides and the least sensitive microbial tests! Labs are losing clients because they are able to detect pesticides at a lower level than other labs. It's a race to the bottom.

As I said in my Sitting Down With interview in the previous issue of The Cannabis Scientist: "Good science is not necessarily the order of the day in the current regulatory framework." And I'll be honest: it's been a somewhat disheartening journey.

What can we do? Well, I now think standardization is looking like a very attractive option. I'm planning to join relevant working groups at the Association of Official Analytical Chemists (AOAC) and American Oil Chemists' Society (AOCS) to help craft the future direction of regulations and testing methodology in our industry. And I urge my science-driven colleagues in cannabis testing to do the same.

Reggie Gaudino, VP R&D, Front Range Biosciences, Lafayette, Colorado, USA

ONLINE

Culture Shock

Microbial safety: why viability testing fails to protect patients.

Kyle Boyar, Field Application Scientist, Medicinal Genomics, Beverly, Massachusetts, USA.

ONLINE

Ethics or Profits?

Lab shopping not only destroys trust in the industry – it also puts consumers in harm's way

Joshua Swider, Co-founder & CEO, Infinite Chemical Analysis Labs, California, USA

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Sampling Standards: The Unspoken Truth

When it comes to the validity of a laboratory result, there are several factors to consider – and these are not always related to the quality of the analytical method. Though often overlooked, sampling is an integral aspect of the cannabis testing process; indeed, it is critical to the validity and comparability of all laboratory results.

In any field or industry, legitimate results or statistically viable groups of data must begin with a representative group of samples. Currently, based on my personal experiences, it is clear that the sampling procedures and methodology in the cannabis industry are vastly inconsistent, which makes the validation and comparison of results particularly difficult – even with access to good analytical technology and methods.

Though sampling cannabis may seem simple, I can assure you that it comes with its fair share of challenges. Cannabis flowers – or more specifically trichomes – contain some of the most desirable, marketable, and tested compounds in the industry: the cannabinoids and the terpenes. The trichome structures are highly fragile and can easily be damaged through variation in pressure, light and temperature. Having said that, it makes sense that the methods by which a grower collects, retains, and sends his cannabis samples to the labs will also have a strong impact on the outcome.

Not being an expert on the subject myself, I decided to contact Hubert Marceau, chemist and Director of Development at Phytochemia, who had this to say:

"As a Canadian lab, we have no control regarding the sampling methods of our customers and must assume that they did their sampling correctly. In reality, we see a large variability in the samples that we receive, due to the individual interpretation of the guidelines. This can create confusion when businesses want to compare themselves to others, since the variation induced by the sampling can sometimes be significant."

Marceau's comment prompted me to investigate even further. The guidelines provided to the producers in terms of sampling are quite generic, undefined, and unregulated, leaving lots of room for interpretation. Human nature being what it is, interpretation rarely goes hand in hand with impartiality – especially in the case of cannabis, where the end results have a huge impact on the commercialization of the products.

To protect consumers and inspire confidence in the community, we're bound to evolve towards the same standards of more mature markets, such as alcohol. So regardless of any challenges, standardized testing methodologies and procedures must be implemented – sampling included – to accurately characterize cannabis in any form and anywhere.

Meanwhile, it is our duty to stay informed and talk about those issues. Only by communicating, sharing opinions, and increasing research will we be able to bring the cannabis market and community to its rightful place.

Mathias Plourde, Biochemist, M.Eng.
Market Specialist, Premier Tech Growers and Consumers

VIEW THE FULL ARTICLE ONLINE

FEATURE

Gurus of Pesticide Residue Analysis

The measurement of pesticides is challenging in itself, but with complex matrices, regulatory inconsistencies and the impact of heating and combustion, cannabis brings its own issues. As regulators in California and elsewhere tighten up pesticide testing rules, we speak to three top scientists about the analytical hurdles that need to be cleared – and the technology required to do it.

How has pesticide residue analysis changed over the last decade?

Jingcun Wu: Traditionally, pesticides were analyzed mainly by GC-MS; however, ionic and polar compounds often require derivatization, and GC-MS is not suitable for thermally unstable compounds because of the high-temperature injector used in GC. In the last decade, more and more polar pesticides have been introduced, because they break down quickly and easily. The diversity of pesticides used in production has made multi-residue techniques the method of choice for more cost-effective and efficient analysis of pesticides in testing laboratories. With the advance of LC-MS/MS technology in the last couple of decades, especially the availability of ultra-high-performance liquid chromatography (UHPLC) and high acquisition speed mass spectrometers with fast polarity switching, UHPLC-MS/MS has become the go-to technology for multi-residue pesticide analysis in food and environmental fields – including cannabis.

Christopher Hudalla: As recently as four years ago, most testing in the cannabis industry was done for marketing purposes, to show that one product would get you more stoned than another. It was not a very robust testing environment… but it is changing dramatically. Everyone in the cannabis industry now realizes how critical testing is for patient and consumer safety. And as each new state implements testing regulations, they set a higher standard. Today, in many states, labs must be ISO 17025 accredited, which means they are forced to validate their methods and document their abilities. A test certificate saying "Avermectin: none detected" is meaningless if it doesn't list the lower limit of sensitivity, or how it was measured – otherwise "none detected" could mean you sniffed it and didn't smell any pesticides!

David Egerton: When testing laboratories were starting out, there was very little funding; many of the first labs simply didn't have the budget to acquire a triple quad MS (or the inclination, as testing was voluntary). Hence, early analyses were largely based on very old methods, such as GC with electron capture detector or nitrogen-phosphorus detector, or single quad MS. A few years ago, many labs started to shift towards triple quads. That's been the biggest innovation in the field, and it's been quite the rollercoaster trying to reconcile all the methods developed in-house over the years, making sure all the labs are operating on an equal footing.

What are the main challenges in pesticide residue analysis – and how can we tackle them?

DE: As with many materials, the matrix is the problem. Unfortunately, cannabinoids elute from chromatographs at around the same time as the bulk of our pesticides. I have not found any solid phases that selectively remove pesticides from cannabis – so commercial cleanup technologies are not always the best solution. Furthermore, the breadth of the pesticides that some regulators have asked us to detect not only necessitate using two instruments – the LC and GC triple quads – but can also create difficulties in designing multi-residue methods. Figuring out a sound chromatographic way to get around the interference created by the cannabinoids would certainly make pesticide analysis – and indeed, many of our other analyses – much easier. The dream for me would be a resin that's specifically tailored to and would only bind cannabinoids – everyone in this industry would love that!

JW: I agree that the main analytical challenge is analyzing multi-pesticide residues at low levels from complex sample matrices. The most efficient approach for a testing lab is the use of multi-residue methods capable of determining many pesticides in one single run, but the differences in regulations among the states make it a challenge to have a single method that meets all the regulatory requirements. To overcome sample matrix effects, numerous tools have been applied to LC-MS/MS method development, such as sample dilution, use of stable isotope internal standards, sample matrix-matched standard calibration, standard addition method, sample clean-up, use of high efficiency UHPLC columns for better separation, and the use of alternative ionization sources. In my view, because of the diversity of sample matrices and the fact that the sample matrix without analytes is difficult to find, the dilute-and-shoot method is the simplest and most cost-effective approach to reduce matrix effects, although this methodology requires highly sensitive and robust instrumentation.

CH: Cost is also a factor – in terms of instrumentation, personnel, and consumables. Unfortunately, there are so many different classes of pesticides, analysis would typically require multiple pieces of instrumentation, most likely a liquid chromatograph or gas chromatograph with a triple quad mass spectrometer. To buy one of each costs close to \$1m. Plus, as David mentioned, matrix interferences are a real problem – so you need highly skilled chemists who can distinguish between interferences and true pesticide contamination. You get what you pay for, and to do this right is expensive.

"As legalization efforts continue, the methods for detecting metals and other contaminants will likely include a greater number of target compounds at increasingly stringent detection limits."

How do you see pesticide residue analysis developing in future?

CH: I think in 5–10 years, pesticide testing in cannabis will be no different than that performed in agriculture. The rapid growth of the cannabis industry is spurring innovation like nothing I've ever seen before. For example, the pharmaceutical industry has seen little improvement in child-proof packaging for decades. Now, thanks to the cannabis industry, the advances in child-proof packaging are astounding. As for analytical instrumentation, we work with a lot of instrument vendors who create prototypes of equipment, and what I see on the horizon for novel technologies is fascinating. LC/MS and GC/MS are not going to go away, but I think there are going to be better, cheaper alternatives in the next few years, driven by the complexity of pesticide testing. For example, the chemical sensors used for homeland security can sniff out chemical profiles with great sensitivity, and I think we'll see them being applied to the cannabis industry. We have been working with many instrument vendors, including 908 Devices on the development of their 3-in-1 Cannabis Analyzer – another potential game changer in terms of speed of analysis, though it can't detect pesticides at this time.

DE: I think we'll see some "evening out" of the regulations. We're always hoping for a standard method to be published, which every lab could follow and have faith in, and I hope we'll see some homogeneity develop between states in time. But with each state driving its own regulations, it's hard to say exactly when…

JW: I would definitely like to see more collaboration among instrument manufacturers, testing labs and regulatory bodies – as well as scientific communities – to develop more reliable methods, and standardize them to better serve our customers' need for safe cannabis products. I'm hopeful that the AOAC and similar scientific organizations will be able to agree standardized methods for multi-residue pesticide analysis and organize meaningful inter-laboratory testing and validation or proficiency testing.

Final thoughts?

DE: Over the years, we've seen major improvements from a number of our clients, and have seen overall failure rates drop from 70 percent to below 50 percent. We've also seen increased awareness of the issue from producers of cannabis oils and edibles, who are driving demand for clean product in both directions – downward to the growers, and upwards to the end users. It's not uncommon for dispensaries to display the Certificate of Analysis (COA) on the shelves next to their products.

CH: Ultimately, this is all about ensuring consumer safety. We work directly with a lot of patients, and our youngest was 13 months old when we started working with her. She has pediatric epilepsy, and my hope is that cannabinoid therapy will continue to control her seizures for decades to come. For long-term patients like her, it's critical that these products are free from contamination.

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Meet the Gurus

Christopher Hudalla, Founder and CSO, ProVerde Laboratories, Massachusetts, USA

Chris worked for Waters Corporation for 14 years before establishing ProVerde Laboratories, Massachusetts, USA, in 2013. He is an experienced separation scientist, with a 25-year career focused on spectroscopic and chromatographic methods, including supercritical fluid chromatography (SFC) and convergence chromatography. He has been a tireless advocate for better quality and consistency for cannabis testing, and serves on a several committees to develop unified standards for the industry.

David Egerton, Laboratory Director, Infinite Chemical Analysis Labs, Michigan, USA

With a BS and MS in Chemistry from the University of Louisville, David initially worked on tissue culture for a clone producer, before joining testing lab CW Analytical in 2011, where he liaised closely with Californian regulators about new testing regulations. Now at Infinite Chemical Analysis Labs in Michigan, David says, "The fun thing about this industry – and being an analytical chemist – is that you are constantly solving puzzles."

Jingcun Wu, Senior Strategic Scientist, PerkinElmer, Canada

Jingcun has worked in analytical chemistry for over 25 years, both in industry and academia – including an adjunct professor position at the University of Waterloo, working with sample preparation pioneer Janusz Pawliszyn. Together with the team at PerkinElmer and a number of outside partners, he has developed methods to determine large numbers of pesticide residues in cannabis in a single run using LC-MS/MS.

SITTING DOWN WITH

Making Cannabis Labs Accountable

Sitting Down With... Susan Audino, ISO Assessor and Instructor, Scientific Advisor at AOAC International CASP, and Chemistry Laboratory Consultant at S.A. Audino & Associates, LLC, Wilmington, Delaware, USA

You had an unusual route into analytical chemistry…

I was originally a psychologist, but after several years working as a counselor in emergency rooms, I was burnt out and ready for a change. I was accepted onto a course to re-train as a chiropractor, provided I first took classes in organic chemistry, biochemistry and physics. I enjoyed my chemistry classes so much that I decided to continue them. I can remember a specific day when I was studying the visible light spectrum in the laboratory and I was filled with fascination about the underlying physics. It sparked a passion for spectroscopy and physical chemistry that eventually led to a new career. While studying undergraduate chemistry, I won an award to do independent research and got the chance to work with the US Secret Service in their forensic chemistry division. After that, I decided to apply for graduate studies in chemistry instead of chiropractic school.

How did you get involved in the cannabis industry?

Around eight years ago, I was working as a chemist in the Department of Agriculture when I got a call from a family friend, who asked me to join the quality assurance team of their up-and-coming dispensary in Rhode Island. My first reaction was that I wanted nothing to do with cannabis, which I believed should be illegal. But the conversation prompted me to start reading about the chemistry of cannabis and I became increasingly intrigued. The turning point came when I met Raphael Mechoulam – the eminent Israeli chemist who discovered the endocannabinoid system – at a conference. He helped to change my mind about medical cannabis, and as I learnt more about the cannabis industry, I became aware of its shortcomings and wanted to make positive changes. Cannabis is an amazing topic – it's economics, law, politics, botany, biology, chemistry and math all rolled into one. There are ups and downs – misconceptions and shortsightedness – but I believe we're moving in the right direction.

Why are standard methods for cannabis testing so important?

As part of my work, I go to a lot of dispensaries. When I flip over a packet and ask the staff what the numbers on the label mean, very few are able to tell me and, even if they can, the numbers don't always add up. Consumers generally trust the information on product labels, but the reality is that we often have no idea. Why? There are no standard test methods for cannabis, so it's impossible to verify test results. We could send one sample to three different labs and get three different results – from three different methods. Though it is worrying that five states require no testing whatsoever, I believe inadequate testing is worse than no testing at all because it gives a false sense of security. Imagine your doctor prescribing 10mg of heart medicine, but the pill turned out to contain 30 mg; you might well end up sicker than if you'd been prescribed nothing. If results aren't reliable and reproducible, then it's irresponsible.

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