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Observations on Supply Chain Management for Cannabis at ASTM 2018 D-37.02 Meeting

Robert L. Stevenson

The supply chain for cannabis products is but one example of the difficulty in providing safe and effective products for a rapidly growing industry (pun intended).

In 2018, cannabis products are entering the U.S. market, but there is little protection of public health. Cannabis products range from hemp used for clothing and rope to psychoactive for recreational use.

Hemp is used for clothing and natural ropes. It is not controversial, except that it is caught up with the DEA Schedule I regulations. Modern instrumentation can quickly demonstrate that hemp phenotypes do not produce significant THC or related psychoactive cannabinoids. There is little street value to hemp. Enlightened governance should recognize that hemp is benign and create a regulatory exception.

Medicinal cannabis products include cannabidiol. On June 25, 2018, the FDA announced approval of Epidiolex from GW Pharmaceuticals for the treatment of seizures with patients suffering from Dravet syndrome and Lennox-Gastaut syndrome. These are rare forms of epilepsy that begin in childhood. Morbidity is high.

There is a large body of mostly anecdotal examples reporting the beneficial therapeutic effects of medicinal cannabis. Cannabis diol (CBD), in particular, is recognized as an analgesic and often as a non-addictive pain reliever. Thus, many see CBD as an off-label alternative to opiates.

Medicinal cannabis seems to be an attractive class of potential therapeutics that can be controlled using existing drug regulations and dispensed with existing prescription protocols.

The third segment is recreational cannabis, which contains high levels of psychoactive cannabinoids, such as THC. In the U.S.A., the federal government seeks to prohibit all cannabis, including hemp and medicinal cannabis. A majority of the states are responding by legalizing medicinal cannabis. Many states are trying to draw a bright line between the existing black market supply chain and the regulated, taxed, and hopefully safer licit supply chain.

Case in point: California has developed an end-to-end supply chain based on licensed businesses regulated by a track-and-trace paper trail. Licensed nurseries must buy the seeds from a registered supplier. Licensed growers must buy their seedlings from licensed nurseries. Licensed processors (for drying, grinding, and packaging, etc.) must buy from licensed growers. Retailers, including dispensaries, can buy only from licensed growers or processors. The goal is to prevent unlicensed suppliers (black marketers) from supplying the licit market.

Interestingly, laboratories are responsible for procuring samples on site. Laboratories, including staff, may not have a financial interest in any stage of the track-and-trace supply chain. Hopefully, being independent will avoid potential problems of data fraud.

Thus, the cannabis world is divided into three parts or market segments. Each has unique market drivers. In the licit drug world, these are called critical quality attributes (CQAs). These often take the form of the desired benefits such as euphoric high, linked to specifications (THC content), but in the reverse order.

For more information see page 10.

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Endocannabinoids Shown to Control Inflammation in Animal Studies

For the first time, researchers have found a biological mechanism to explain why some marijuana users have reported beneficial effects from cannabis on intestine inflammation conditions such as ulcerative colitis and Crohn's disease.

University of Massachusetts Medical School scientists discovered that gut inflammation is regulated by two important processes, which are constantly in flux and responding to changing conditions in the intestinal environment. The first process promotes an aggressive immune response in the gut that destroys dangerous pathogens, but which can also damage the lining of the intestine when immune cells attack indiscriminately. The second pathway turns off the inflammation response via special molecules transported across the epithelial cells lining the gut by the same process already known to remove toxins from these cells into the intestine cavity. Crucially, this response requires a naturally produced molecule called an endocannabinoid, which is very similar to cannabinoid molecules found in cannabis.

If the endocannabinoid is not present, inflammation is not kept in balance and can go unchecked, as the body's immune cells attack the intestinal lining.

The researchers believe that because cannabis use introduces cannabinoids into the body, these molecules could help relieve gut inflammation, as the naturally produced endocannabinoids normally would.

Defining Cannabis Standards in a Green Market

David Egerton

Independent cannabis laboratories provide quality assurance to the medical and recreational cannabis market in the same manner that independent quality assurance labs nationwide help to guarantee the safety of foods, medicines, and manufactured goods. Cannabis testing labs receive samples from commercial growers, producers of concentrated extracts (oils), and makers of infused products. Depending on the state requirements for compliance and customer interest, these products are assayed for microbiological contaminants, cannabinoid concentrations, pesticide residues, residual solvents and/or terpenes. Although some of the analytes are common among QA labs, a number—such as the cannabinoids—are uniquely associated with cannabis. Methods used for the analysis of cannabinoids are often developed and validated by the individual labs. More common analytes, such as fungi, bacteria, and pesticide residues, are often assayed using existing techniques, with some modifications to account for the unique matrix effects and desired list of target compounds.

Standard methods offer an ideal solution for many laboratories by providing a route to expedited method development. By definition, standard methods have undergone validation studies that compare the results between multiple labs, instruments, and analysts. Because of the inherent rigor and peer review associated with this process, these methods provide a turn-key solution that allows laboratories to confidently test for analytes with an abridged validation process. These methods—offered by organizations such as the Food and Drug Administration (FDA), Environmental Protection Agency (EPA), Association of Official Analytical Chemists (AOAC), American Society for Testing and Materials (ASTM), and many others—allow consumers to easily compare labs and impart a degree of confidence in testing. This is a benefit that has thus far been unavailable to operators of cannabis laboratories.

Challenges to cannabis analysis

Due to federal restrictions, extracts and materials containing the active ingredient Δ9-tetrahydrocannibinol (d9-THC) or other cannabinoids are not permitted for transport without a Drug Enforcement Agency (DEA) exemption. This prohibition impacts laboratories attempting any kind of nationwide proficiency testing (PT) as well as national interlab comparisons for the development of standard methods. Proficiency testing can be conducted, but never in the same matrix as the samples received by cannabis labs. Providers of these PTs must therefore offer the samples either in a premade solution or in some matrix determined to be similar to the cannabis

flower. The American Oil Chemists' Society (AOCS) and Emerald Scientific (San Luis Obispo, CA) have developed a PT for many of the analytes assayed by cannabis labs, but they are not offered in the correct matrix. While invaluable for assessing the calibrations in use in cannabis labs, the test does not assess sample preparation. Certified reference material (CRM) producers offering a DEA-exempt standard are only able to offer materials at concentrations of 1.0 mg/mL or less, limiting their use in spike recovery.[1] Despite the fact that over 100 cannabinoids have been identified in cannabis, fewer than 20 of these compounds are available commercially.

Cannabis offers a unique challenge in regard to contaminant testing due to inapplicable target lists. For example, USP <467> describes testing for residual solvents on pharmaceuticals and establishes maximum residue limits (MRLs) for each solvent. Low-molecular-weight hydrocarbons (LMW HCs) are not included in this list (such as propane, n-butane, and isobutane) and therefore default to a 5000-ppm limit according to this document. Although all of these compounds enjoy a G.R.A.S. (Generally Regarded as Safe) status with the FDA, these hydrocarbons are routinely used in the manufacture of concentrated cannabis oils and their residues are of particular interest to the industry. Regulations designed specifically for the cannabis industry[2] have identified this, and many have created MRLs for these LMW HCs while taking limits on other residues directly from USP <467>.

Multiresidue methods for pesticide residues are readily available, but rarely do they include all residues of concern to the cannabis industry. Modifications are thus usually made to existing methods and are validated by each laboratory. This lack of uniformity in the methods utilized is often confusing to the consumer, and leads to highly varied target lists from the different labs. Limits of detection and quantification are also typically different, leading to situations in which the same material may pass a test in one lab but fail in another. There is no analogous agricultural commodity with established pesticide MRLs in line with cannabis. Tobacco may seem like an obvious choice, but the FDA and EPA have declined to establish MRLs for domestically grown tobacco.[3] Lacking this information, regulators and cannabis lab operators are left to determine what constitutes a safe residue level. Some states, such as Oregon, have taken a proactive approach, creating a clearly defined target list that includes most of the analytes in common use during cannabis cultivation. In some cases the language is vague, stating that the material should be tested for chemical contaminants without providing an MRL or target list.

Cannabis labs are routinely confronted with clients that have a poor understanding of variation within natural products. Because most states do not have a provision for laboratories to perform sampling themselves, it is up to the client to collect the samples and provide them to the lab. Due to the high monetary value of the material, these samples are often the bare minimum needed to conduct the test, leading to predictably wide variability between sample submissions. When combined with the use of different methods and instrumentation, there is very little baseline for understanding whether the source of the bias is from the laboratories or the sampling.

Efforts to date

Since 2011, the Association of Commercial Cannabis Laboratories (ACCL) has been advocating for its members and greater unity in methodologies.[4] Regular proficiency testing, managed by Emerald Scientific and the AOCS, provides an additional measure of credibility to members. Efforts are underway to develop standard methods through ACCL and

AOAC, and members are typically willing to share extraction techniques and calibration methodologies.

Since the first laboratories began operating in 2007, the provisioning of certified reference standards that are tailored to the cannabis industry has progressed substantially (*Table 1*). The growing availability of individual and mixed standards has proceeded in step with the technological improvements of the lab industry and increasing specificity in state regulations. As the number of labs and the desire for QA testing has become routine, the number of providers fulfilling this niche has increased.

Cannabis labs are more accurate and robust in their capabilities than ever before, as demonstrated by proficiency test results. The impression in the industry that labs are highly variable in their results stems directly from the aforementioned reasons, but the fault is often placed on the laboratory. Much of this comes from lack of client fluency in reading and understanding technical data and the inherent variability in analytical results. It is incumbent upon all labs to educate their clientele about natural variability without pushing the blame onto a competitor. Cooperation between competing labs can only lead to improved precision and better agreement between different methods.

Cannabis labs have spent years optimizing their methods for a wide variety of matrices without the benefit of tailored reference standards, application notes, or white papers. This is now changing, as public acceptance of cannabis is growing, and more equipment manufacturers and trade groups are seeing opportunity in this bourgeoning industry. These resources, produced by companies such as Restek, Cerilliant, Sciex, Shimadzu, and others, have provided the first steps in achieving greater credibility in the industry. Cannabis laboratories and trade groups such as the ACCL are doing their part by attaining ISO 17025 accreditation and adhering to good laboratory practice in an effort to improve the image that has been unfairly applied to them. As the cannabis industry matures, labs can be expected to more closely resemble their counterparts in the environmental testing industry.

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Table 1 - Changes in availability of certified reference materials from 2009 to 2016

	2009	**2016**
Cannabinoids	3	~20
Terpenoids	Individual	Mixes containing >30 compounds relevant to cannabis
Residual solvents	Mixes based on USP <467> classes; none for LMW HCs	Tailored to industry, including LMW HCs
Pesticides	Individual; EPA method-based mixes	Tailored to state regulatory lists for cannabis

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Stability of Licit Cannabis Products

Robert L. Stevenson

The licit commerce of cannabis products is based on expectations of their safety and efficacy. Consumers expect that the products will be distributed much as other drugs and edibles, in a package with known potency and assurance of safety and efficacy. Further, they will expect the products to be stable enough for use. Statements of manufacturing date, shelf life, and use-by dates will thus be required.

Some cannabis products involve processing that entails adding a fraction of cannabis to another matrix such as cookies, candies, salad oil, etc. These new formulations are often not characterized. Today, stability of the product is seldom considered. This will change with experience.

In contrast, stability is a major consideration in preparing a drug for market approval. Formulation labs are tasked with engineering the active pharmaceutical ingredient (API) to meet the critical quality attributes while simultaneously meeting the idiosyncrasies of the distribution system from origin to the patient. Factors include container, closure, labeling, drug form (pill, injectable, topical, spray), excipients, storage conditions, degradation products, impurity profile, shelf life, and more.

How should one deal with stability when cannabis products are so varied and poorly characterized? Let's start with the critical quality attributes (CQA), which are product-dependent (*Table 1*).

The recreational market is the most complex. Products range from flowers and leaves from a wide range of poorly characterized phenotypes to extracts and oils. Processed plants are often smoked or vaporized. Extracts are used to add THC and perhaps flavor to candies, oils, and baked goods.

Traditionally, recreational users have relied on the black market. Products were seldom characterized. Packaging was often a plastic bag. Labeling was minimal and not traceable. Other potential contaminants such as pesticides, microbe toxins, trace metals, and solvents were ignored.

Replacing the black market with a licit supply chain is the task at hand. Fortunately, there is a lot of precedence. In the U.S.A., due to the Schedule I classification, the federal government is not participating—and indeed is antagonistic to—cannabis commerce. But, other countries, such as Holland and Canada, and a majority of American states recognize the need for science-based regulation of the cannabis industry. However, each program

Table 1 - Market segmentation for cannabis products

Market segment	API	CQA
Recreational	THC	"Euphoric high" and flavor from terpenes
Medicinal	Diol and acid	Pain relief, epilepsy
Hemp	Fiber	Strength, clothing

seems different, and some are in conflict. There is a need for harmonization. Since the harmonization is unlikely to come from the American government, ASTM International is working with other standards institutions such as the U.S. Pharmacopeia and the American Herbal Products Association (Silver Spring, MD) to create appropriate, harmonized, regulatory science-based data required for cannabis commerce.

I've been asked to lead a small task group in ASTM D-37 to develop documents related to the stability of cannabis products. Anyone interested in helping can contact me at rlsteven@comcast.net; tel.: 925-283-7619.

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HPLC Rapidly Measures Phytocannabinoid Potency

While traditional cannabis potency tests can take up to 20 minutes to perform, a new test measures phytocannabinoids in under seven.

According to chemistry student Matthew Noestheden at The University of British Columbia Okanagan Campus, the substance can be tested in record time and can identify a virtually limitless number of phytocannabinoid variants.

"Most people are familiar with THC as the primary bioactive compound in cannabis. But in reality, there are more than 100 different phytocannabinoid variants, many with their own unique biological effects," said Noestheden. "The problem is that it's very difficult to differentiate between them when testing cannabis potency."

The team used a high-pressure liquid chromatograph to isolate each phytocannabinoid to measure them independently. They were able to discern the potency of 11 unique phytocannabinoids in cannabis extracts, which is important for determining the safety and authenticity of cannabis products.

"We tested twice as many phytocannabinoids compared to what most labs are testing for now, and more than twice as fast," Noestheden noted. "We limited our tests to 11 variants because these were the only ones commercially available at the time. We could just as easily test for 50 or even all 100 variants, including some synthetic cannabinoids that can be added to products to increase potency."

A Multiplatform Approach to Residual Pesticide Quantitation in Cannabis Flower for the California and Canadian Target Lists

Anthony Macherone, Rick Jordan, Dan Miller, Lilly Asanuma, Jean-François Roy and Peter J. Stone

The legalization of medicinal and recreational cannabis and cannabinoid products by states in the U.S. and Canada has created the need for safety, quality, and regulatory compliance testing prior to retail distribution. Each individual state that has some form of legalization has enacted regulations pertaining to safety and compliance testing. In Canada, medicinal cannabis has been regulated at the federal level for more than a decade. Recreational cannabis legalization is expected to occur in Canada soon and similarly will be regulated at the federal level.

For both states where either medicinal or recreational cannabis is legalized and Canada, chemical classes commonly measured in cannabis and related products include: psychoactive Δ^9-tetrahydrocannabinol (THC) and other cannabinoids, terpenes, volatile solvents commonly used in manufacturing processes, residual pesticides, toxic metals, and mycotoxins. Other common tests include screening for microbial contamination, water activity, and moisture content.

Although there is a general commonality to the testing, each individual U.S. state and Canada has a unique set of target chemicals in each category and action levels for which these chemicals cannot exceed. Proper chemical analysis of these chemotypes requires a suite of analytical systems ranging from high-pressure liquid chromatography (HPLC) with ultraviolet (UV) detection to more sophisticated liquid and gas chromatography triple-quadrupole mass spectrometry systems (LC-MS/MS and GC-MS/MS).

Potency testing measures THC and other cannabinoids and is always required. Terpene profiling, although not required by every jurisdiction, provides information about the cultivar and the organoleptic properties of the product. Unless the measured potency level is out of specification with the product label or mandated level, terpenes and potency measurements will not remove a product from the retail sales stream. In contrast, contamination with pesticides, heavy metals, certain microbes, myco-

toxins, or residual solvents can result in the failure of an entire product lot at substantial costs to growers and producers.

Of all the mandated safety and compliance tests, residual pesticide analysis is particularly challenging primarily because the amounts of pesticides retained on the plant are extremely low compared to the amounts of endogenous chemicals like cannabinoids, terpenes, flavonoids, and chlorophyll, and these "co-extractives" interfere with accurate measurement. This article will describe methodologies for residual pesticide analyses in cannabis flower with an emphasis on the larger target lists of Canada and California.

Comprehensive residual pesticide quantitation in cannabis flower

A comprehensive approach to pesticide residue analysis in cannabis flower included a single sample preparation scheme shunted to both LC-MS/MS and GC-MS/MS for the analysis of more than 210 pesticides.[1] The sample preparation strategy resulted in injecting 500-fold dilutions of the weighed sample into each analytical instrument. Using highly dilute sample extracts, the researchers leveraged the sensitivity and specificity of the analytical platforms and maintained performance for extended periods, thus reducing instrument downtime and increasing productivity. The reported method included 215 target pesticides with 141 being analyzed via LC-MS/MS and the remaining 74 by GC-MS/MS. Method performance was demonstrated by injecting five replicates at the limit of quantitation (LOQ, determined as signal-to-noise >=10:1). Recoveries between 70 and 120% were determined for 72/74 compounds, and the percent root mean square (%RSD) was less than 15% for all GC-MS/MS amenable compounds. For the LC-MS/MS compounds, recoveries of 70–120%, and %RSD <15% were determined for 138/141 of the target pesticides. An LOQ of 0.1 mg/kg was determined for all but 17 of the 215 targets. For more details see Ref. 1.

Residual pesticide testing in cannabis flower in Canada and California

With respect to the number of target pesticides and action levels, Canada has the most comprehensive list of 95 pesticides with action levels as low as 20 parts-per-billion (ppb) for dried cannabis, and 10 ppb or fresh (wet) cannabis or cannabis oils. The California list is currently the largest in the U.S., with 66 target pesticides and action levels down to 100 ppb for inhalable cannabis and other cannabis products. The Canadian list does not completely incorporate the California list with captan, chlordane, dimethomorph, and fenhexamid unique to California.

The most common analytical platform for the quantitation of residual pesticides in cannabis is LC-MS/MS, and for most U.S. states, including the 59 target pesticides in the Oregon list, this is exactly true. Except for California and Nevada (as of the date of this writing), all U.S. state pesticide lists can be analyzed using LC-MS/MS only. The Canadian list further presents at least six compounds that are not amenable to common LC-MS/MS ionization sources such as electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI). These are: endosulfan-alpha and beta, etridiazole, fenthion, kinoprene, and pentachloronitrobenzene. The reasons these compounds do not ionize, or poorly ionize in ESI or APCI, are varied and complex, but may be due to low chemical polarity, thermal instability, dissimilar proton affinities, or the absence of atoms in the structural configuration amenable to the gain or loss of a proton. However, the compounds listed above and

others such as captan and chlordane are commonly, and quite successfully, analyzed via GC-MS/MS using electron ionization. *Figure 1* illustrates a GC-MS/MS chromatogram collected on the Agilent 7890B/7010 GC-MS/MS system (Santa Clara, CA) for compounds contained in the Canadian and California lists that are better analyzed via gas-phase technologies.

When presented with the target lists of Canada and California and the physicochemical properties of the pesticides in those lists, experienced laboratorians immediately recognize that no single analytical platform can properly identify and quantitate the compounds in the complex cannabis matrix without compromising the end results. Simply diluting samples 50-fold in an organic solvent and injecting into a highly sensitive LC-MS/MS that "detunes" the response of most of the pesticides[2] may result in ESI or APCI detection, but only at the cost of increased maintenance and decreased productivity. Another caveat of a single-platform LC-MS/MS approach is the use of a multimode source at high temperatures. Many ESI pesticides in the state lists are thermally labile, and therefore must be ionized at the lowest possible temperatures to achieve sensitivity. APCI requires higher temperatures to work properly—maybe as high as 450 °C. These two disparate properties are incompatible in a single method. Therefore, two different methods taking 30 minutes in total are required. Following this approach, a laboratory would need three LC-MS/MS systems to achieve the throughput of the comprehensive pesticide method presented above. This estimate does not incorporate the increased need for instrument maintenance that results from injecting large volumes of high-matrix samples, which will further reduce productivity and revenue generation.

Increasing productivity by including mycotoxins in the LC-MS/MS residual pesticides test

When run in parallel, analytical cycle times of 10 minutes or less will result in 5–6 samples per hour—essentially triple that of a single-platform approach. To further improve throughput, mycotoxins such as aflatoxins b1, b2, g1, g2, and ochratoxin should be added to the LC-MS/MS pesticide method, thus negating the need for a separate analysis. *Figure 2* shows the analysis of the California pesticide list and five mycotoxins collected on the Agilent Infinity II Prime/Ultivo LC-MS/MS system.

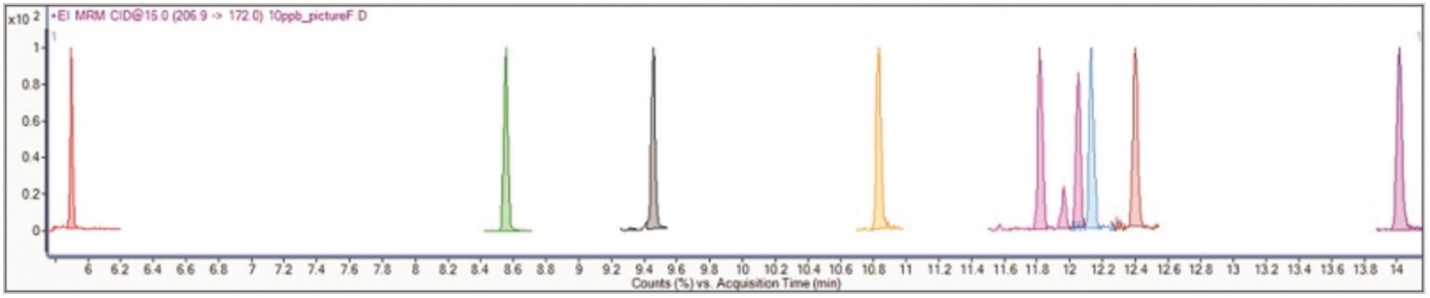

Figure 1 – GC-MS/MS MRM chromatogram. From left to right: etridiazole, pentachloronitrobenzene, kinoprene, fenthion, chlordane cis- and trans-isomers (pink, slight isobaric impurity noted at approx. 12 minutes), endosulfan-alpha, captan, and endosulfan-beta. All concentrations were 10 ppb in dry cannabis flower matrix. The y-axis is scaled to 100%. (Unpublished data courtesy of Jean-François Roy, Agilent Technologies, Santa Clara, CA.)

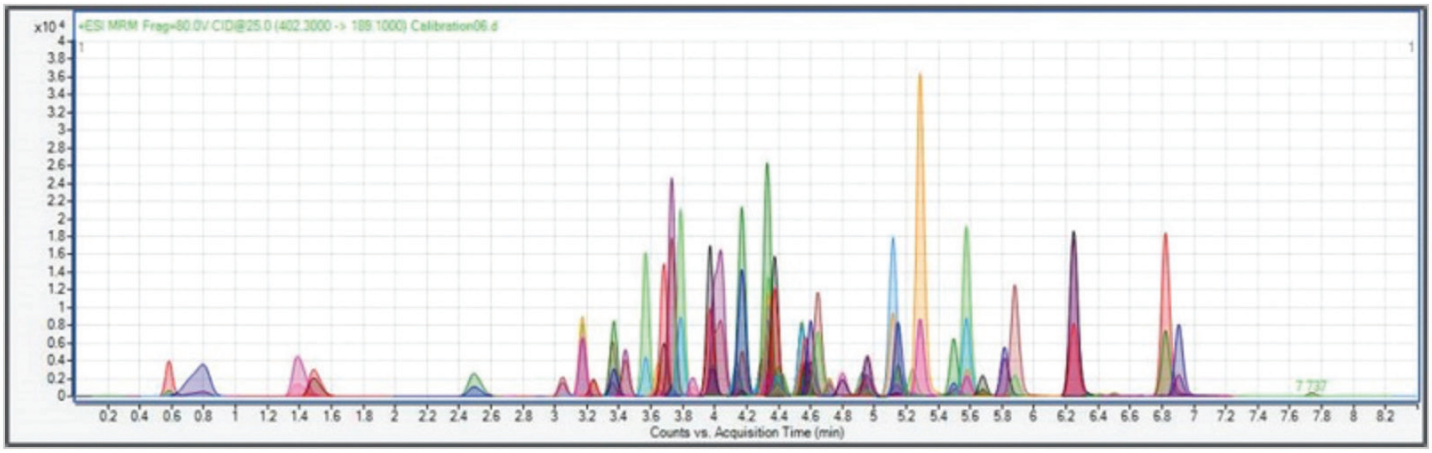

Figure 2 – LC-MS/MS analysis of the California target list plus aflatoxins b1, b2, g1, 2, and ochratoxin. (Unpublished data courtesy of Peter J. Stone, Agilent Technologies, Santa Clara, CA.)

Conclusion

A single-stream extraction followed by 500-fold sample dilution factors analyzed by both LC-MS/MS and GC-MS/MS leverages the benefits of each analytical platform. This approach improves quantitative accuracy and precision and decreases the need for instrument maintenance. Combined, these advantages result in fewer samples requiring reanalysis and increased throughput and revenue generation. Experts in organizations such as AOAC agree that a multiplatform approach is required to quantitate residual pesticides in the various cannabis and cannabinoid matrices, and compounds such as pentachloronitrobenzene, chlordane, captan, and at least two dozen other pesticides included in the various target lists should be analyzed by GC-MS/MS technologies. The ability to orthogonally confirm and quantitate compounds amenable to both platforms, with no reduction on performance, further demonstrates the benefit of a multiplatform approach. Moreover, laboratories equipped with both state-of-the-art LC-MS/MS and GC-MS/MS possess the analytical resources to rapidly and efficiently adapt to a perpetually changing regulatory environment.

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