ADVANCING THE ANALYSIS OF PESTICIDES AND OTHER CHEMICAL RESIDUES
The presence of pesticides and other chemical contaminants in food and dietary supplements is an important concern for both health and environmental reasons, and is receiving increasing scrutiny worldwide. For 53 years, the North American Chemical Residues Workshop (NACRW), formerly known as the Florida Pesticides Residues Workshop, has served as an important forum for disseminating new methods and best practices for detecting and quantifying these contaminants in a wide variety of challenging matrices.

This year, the organizers of the NACRW have collaborated with *LCGC* to bring you this new e-book. In it, four leading experts in the field, all frequent speakers at the conference, share some of their latest work and findings. It makes an excellent companion piece for conference attendees, and for those who cannot attend, it provides an excellent overview of several key topics on the agenda.

First, André de Kok of the Netherlands Food and Consumer Product Safety Authority (NVWA) discusses advances in pesticides analysis using liquid and gas chromatography combined with mass spectrometry (LC–MS and GC–MS), and how to bring the latest developments to routine testing applications.

Next, Sheri Turnipseed of the Animal Drugs Research Center of the U.S. Food and Drug Administration considers the importance of analyzing veterinary drug residues in food, the use of different types of instrumentation, and the role of targeted, semitargeted, and nontargeted screening.

Alexander J. Krynitsky, formerly with the U.S. Food and Drug Administration, then discusses his work to develop effective methods to detect and measure contaminants in dietary supplements, including a method to quantify 96 contaminants in a range of matrices.

We close the e-book with an interview with Steven J. Lehotay of the United States Department of Agriculture’s Agricultural Research Service about work practices and approaches that food analysts need to consider to ensure excellent results in what are often challenging conditions.

We hope you enjoy this e-book, and find it helpful in your work in the analysis of pesticides and other chemical residues.
ADVANCING THE ANALYSIS OF PESTICIDES AND OTHER CHEMICAL RESIDUES

Pesticide Residues
Advancing the Analysis of Pesticide Residues in Food with LC–MS and GC–MS
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Ensuring Accuracy
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An Interview with Steven J. Lehotay
The analysis of pesticides and other chemical residues has advanced significantly in recent years, through developments in methods for liquid chromatography (LC) and gas chromatography (GC), mass spectrometry (MS) detection, and sample preparation approaches. André de Kok, PhD, a senior analytical chemist at the Netherlands Food and Consumer Product Safety Authority (NVWA, Wageningen, The Netherlands), has been focused on moving those methods forward and on bringing the latest developments to routine testing applications. He recently spoke to us about this work.

What do you consider the major trends in methods for the analysis of pesticides and other contaminants? During the last decade, GC– and LC–MS-MS triple-quadrupole instruments have become the standard for quantitative multiresidue methods for the analysis of pesticides and other residues or contaminants. The triple quads have gained their popularity due to their high sensitivity and selectivity and the increased scan speed and robustness of the instruments, allowing the simultaneous detection of several hundreds of analytes in routinely applied methods. Despite the ever increasing scan speeds of recently introduced triple quads, however, the main disadvantage is still the fact that MS-MS triple-quadrupole methods are targeted methods aimed at detecting a limited scope of analytes.

High-resolution (accurate mass) mass spectrometers, based on the time-of-flight (TOF) or orbital trapping principle, operating in the full-scan mode, have an essentially unlimited scope and can perform both targeted and untargeted analysis. Therefore, they are becoming increasingly popular and are finding their way into research laboratories, but also slowly into the routine laboratory. In pesticide residue labs, LC–high-resolution mass spectrometry (HRMS) methods are mainly used in the targeted mode, where...
the scope is determined by the number of pesticides available in the database library. A nice aspect of LC–HRMS methods is the possibility of alternatingly using the full-scan and MS-MS modes in the same chromatographic run. This capability further increases the selectivity and sensitivity of the detection method.

We recently acquired a high-resolution quadrupole time-of-flight (QTOF) instrument with a resolving power up to 50,000 (at m/z 800), and have developed in our laboratory an ultrahigh-pressure liquid chromatography (UHPLC)-QTOF method for the targeted analysis of over 500 pesticides. We have fully validated the method initially for 155 pesticides in the representative matrices lettuce and orange.

Soon we will also acquire a new GC–HRMS instrument after finalizing the European tender procedure. This system will complement our UHPLC-QTOF instrument and the routine GC– and LC–MS-MS triple-quadrupole methods.

Remaining challenges to be addressed in the coming years include further optimization of the software methods by the HRMS vendors and the validation of high-resolution methods for use in routine applications. Guidance criteria for identification and quality control procedures for routine analysis will have to be adapted specifically for high-resolution methods.

You participated in an interlaboratory study involving quantitative LC–MS–MS analysis of 120 pesticides in 21 fruit and vegetable matrices (2). Five laboratories with five different LC–MS-MS systems contributed to the study. What sample preparation approach was used for this study, and why?

We used a QuEChERS (quick, easy, cheap, effective, rugged, and safe)-type acetonitrile extraction with magnesium sulfate as a partitioning salt to induce a good phase separation. No cleanup was applied, because it is usually not necessary when applying LC–MS-MS detection methods. The main aim of the interlaboratory study was to evaluate the European Union Analytical Quality Control (AQC) SANCO document identification criteria for LC–MS-MS triple-quadrupole methods. In the older version of the document, the tolerance for the ion ratio (the difference obtained for the sample extract and standard) was set depending on the value of the ion ratio, where the tolerance increased from 10% to 50% with a decreasing ion ratio range from 0.5–1.0 to <0.1. In the study, it became clear in all five laboratories that the variability of the ion ratio does not depend on the absolute value of the ion ratio, but on the absolute response of the least-intense ion detected. As long as the response of the least-intense ion is above the quantitation limit, the ion ratio remains stable. This justifies setting an ion ratio tolerance at a fixed value.

The study looked at two important criteria for pesticide identification:
retention time and ion ratio. What conclusions did you draw from the results of the study regarding false-positive and false-negative identifications? The percentage of false positives and false negatives depends on the tolerance levels set for both the retention time window and the ion ratio. The higher the tolerance is set, the higher the percentage of false positives, and the lower the tolerance level, the higher the false negatives. Decreasing the retention time window considerably decreases the percentage of false positives. Because the retention times are very stable in modern UHPLC systems, an absolute retention time window tolerance of ±0.1 min can easily be set. This is a more practical and realistic tolerance than the old percentage tolerance depending on the retention time. Furthermore, we found that we could set a practical uniform ion ratio tolerance of 30%, which resulted in no false positives and a false negative rate of <5% for all tested pesticide-concentration–matrix combinations. The new identification criteria are now included in the newest version of the EU Document (2), No. SANTE 11945/2015 (Implemented on January 1, 2016).

The study also underlines the importance of including validation of method identification limits and ion ratios during method validation studies. It is important to add that the criteria are guidance criteria that always have to be applied in combination with the expert judgment of the analyst. Your group worked on miniaturizing and optimizing a sample preparation method known as the Dutch “mini-Luke” method (3), that originated from the method developed in 1975 by Luke and colleagues and had been steadily improved over the past few decades. Can you please briefly describe the mini-Luke and new mini-Luke method (NL method) for multiresidue pesticide extraction from fruits and vegetables and how it differs from other methods such as QuEChERS?

In the early 1980s, we developed the Dutch mini-Luke method as a very fast and efficient wide-scope extraction method for hundreds of pesticides in fruits and vegetables using both selective GC detection (such as electron-capture, nitrogen–phosphorus, and flame photometric detection) and LC detection (fluorescence and diode-array detection) and later also using full-scan GC with ion trap detection (GC–ITD). The method uses acetone as the basic extraction solvent and dichloromethane and petroleum ether as partitioning solvents, in the presence of sodium sulfate. A 15-g sample was extracted with 30 mL of acetone and partitioned with 30:30 mL of dichloromethane–petroleum ether (+15 g Na₂SO₄). In the new mini-Luke method (now called the “NL method”), the solvent use is further decreased to 20 mL of acetone and 10:20 mL dichloromethane–petroleum ether. However, the solvent use is higher than with the QuEChERS
method (based on acetonitrile extraction), but this NL method allows the use of direct, very fast and efficient (two times 30 s) Ultra-Turrax (IKA) homogenization and mixing, resulting in optimum extractability of incurred pesticide residues in even the most difficult or voluminous (dry) matrices.

A 15-g test portion of the laboratory sample, in combination with Ultra-Turrax mixing, is usually more representative and leads to a lower sample processing error than the 10-g test portion usually used in the QuEChERS extraction method, when only ambient homogenization, and not cryogenic milling, is being applied, in combination with hand shaking or short mechanical shaking times. In most laboratories, cryogenic milling is not routinely used, especially not in labs where 8-h turnaround times are required by clients. Another difference with the QuEChERS method is the use of an evaporation step for the extract in the NL method. This step takes some extra time, but it allows the use of an optimal injection solvent for both LC (methanol) and GC (isooctane–toluene). Particularly for storing of extracts for GC analysis, this is a major advantage for GC-injection-labile compounds like captan, captafol, folpet, dicofol, and chlorothalonil. The NL method showed equivalent recoveries to the Dutch mini-Luke method and has been implemented in routine analysis without any problem.

What changes did you make to the method to miniaturize it, and what were the benefits of that miniaturization? Were recoveries affected by the changes to the method? The solvent volumes (and thus the costs of the analysis) were further reduced (as described above) and the use of dichloromethane was able to be minimized, although not eliminated, while still obtaining acceptable recoveries for the most polar pesticides. The NL method showed equivalent recoveries to the Dutch mini-Luke method and has been implemented in routine analysis without any problem.

You developed a GC–MS method for analyzing 51 pesticides in green coffee beans (4). What challenges did you face in finalizing the sample preparation steps for this method? In this study, we used an acetonitrile-based extraction method, because we also had to concurrently conduct LC–MS analysis of pesticides and mycotoxins (unpublished results).
Coffee is a very difficult matrix, especially for GC–MS analysis. Therefore, we developed a GC–MS method using negative chemical ionization (NCI), using the single-ion monitoring (SIM) mode, and recently a GC–MS-MS method using NCI (unpublished results). These methods are complementary to our standard GC–MS-MS method using electron ionization (EI). NCI–MS is a very sensitive and selective detection method, which is specifically favorable for difficult matrices. Complementary use of EI–MS-MS and NCI-SIM-MS or NCI–MS-MS can reduce the chance of false positives and false negatives. For sample extract cleanup, the use of just a simple dispersive SPE step with C18 sorbent was sufficient to obtain acceptable recoveries and good repeatability relative standard deviation (RSD) values, with method limits of quantitation (LOQs) of 10 ppb for almost all tested pesticides.

How did you overcome the high matrix effects you encountered in that study—even after the sample cleanup steps—to make the method useful for reliable quantitation and routine analysis?
High matrix effects are quite common for GC methods, but in this case the matrix effect was positive (response enhancement), which has as an advantage that the detector response is higher for sample extracts than for standards in solvent, resulting in better detectability of the pesticides and thus lower method LOQs. The use of matrix-matched standards guarantees reliable quantitative results in routine analysis.

A recent study performed by your laboratory examined the optimization and validation of an UHPLC–MS method for determining the herbicides paraquat and diquat in cowpeas (5). What are the challenges of analyzing paraquat and diquat, and how does your method overcome those challenges?
Because of their ionic characteristics and high polarity, the herbicides paraquat and diquat cannot be analyzed by multiresidue methods, and require a dedicated single-residue method. The best extraction solvent mixture is methanol–water, but the pH during extraction also plays a crucial role, especially for difficult, dry matrices like cowpeas containing incurred residues. The use of 0.5 mol/L HCL in the extraction solvent mixture (1:1 [v/v] methanol–water) and an additional heated extraction step at 80 °C for 15 min was necessary to obtain optimum extraction efficiency. The use of isotopically labeled internal standards used during the whole procedure was also required to obtain reliable quantitative results.

How did the method perform in field trials in which samples were collected from plots that had been sprayed with the herbicides?
The developed method for paraquat and diquat was successfully applied to the analysis of real samples originating from field studies where the herbicides had been applied in different regions, under different weather conditions, and with the herbicides applied in different growing stages.

What are the next steps in your research on pesticide analysis?

Our new research projects focus on new extraction approaches. In our LC methods, we are trying to include a wider range of polarities of LC-amenable compounds in one multiresidue method by direct injection of acetone extracts. For our GC methods, we are trying to further optimize the partitioning solvents to obtain even cleaner extracts for GC-amenable extracts. For both the LC–MS and GC–MS methods, such developments would allow us to eliminate the evaporation steps. This will lead to the fastest possible extraction procedure, with the widest possible scope for both GC- and LC-amenable pesticides.

Our research on detection methods will be further focused on developing, optimizing, extending the scope of, and validating and implementing GC– and UHPLC–HRMS methods in routine use. The ultimate aim is to fully replace our GC– and UHPLC–MS–MS triple-quadrupole methods by GC– and UHPLC–HRMS methods.

And even though the optimized and extended multiresidue methods will always be the basic methods for pesticide residue laboratories, some single-residue methods will still be necessary and have to be further optimized for robustness for routine application.

Finally, the scope of the methods can be extended to other contaminants like mycotoxins and veterinary drugs. The biggest challenge here will be the logistics of sampling programs and laboratory procedures. We will need integrated sample preparation and sample processing and will have to bridge the knowledge of different teams and disciplines.

References

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Advancing the Analysis of Veterinary Drug Residues in Food

An Interview with Sherri B. Turnipseed

Testing for veterinary drug residues, such as antibiotics, in food, is critical to reduce risks to human health and to the environment. Sherri B. Turnipseed, PhD, a research chemist in the Animal Drugs Research Center of the U.S. Food and Drug Administration, has done extensive work in this area. In this interview, she spoke to us about the importance of such testing, the use of different types of instrumentation, the role of targeted, semitargeted, and nontargeted screening, and other aspects of this work.

How serious or widespread a problem is the presence of veterinary drug residues in aquacultured fish and shellfish? And how diverse are the compounds that need to be detected when screening for drug residues? Veterinary drugs, including antibiotics, are commonly administered to fish raised in captivity to treat disease or proactively prevent infection. The list of drugs approved for use in aquaculture and the allowable maximum residue limits in fish tissue varies by country (1). A primary concern with the use of antibiotics in aquaculture is the potential for increased antimicrobial resistance. Other chemicals, such as chloramphenicol or the triphenylmethane dyes used as antifungal agents, also have potential adverse human health effects and are prohibited for use in food animals. Nevertheless, residues of these compounds and other drugs are continually found in fish and shellfish. The types of antibiotics, anthelmintics, and antifungal drugs used in the aquaculture industry represent many classes of compounds, including sulfonamides, tetracyclines, β-lactams, macrolides, avermectins, triphenylmethane dyes, phenicols, fluoroquinolones, nitrofurans, nitroimidazoles, and benzimidazoles. Consequently, developing a method to screen for these diverse analytes at residue levels in complex fish and shellfish matrices can be very challenging.
When analyzing veterinary drug residues in aquacultured products, what are the advantages of using high-resolution mass spectrometry (HRMS) techniques? Are there any disadvantages?

The primary advantage of using HRMS methods is that an unlimited number of compounds can be analyzed simultaneously because full-scan data are collected, rather than preselected ion transitions corresponding to specific compounds. Selectivity and sensitivity are achieved by taking advantage of the instrument’s ability to provide very accurate mass measurements. This capability leads to the development of methods that can detect a wide range of residues and contaminants, allowing regulatory agencies to be more proactive in discovering possible adulteration of aquacultured products. A disadvantage is that HRMS screening methods may not be as sensitive for any given analyte as compared to a liquid chromatography (LC)–MS-MS method using a triple-quadrupole mass analyzer specifically optimized to maximize signal for each compound.

With HRMS methods, one can conduct several types of qualitative screening methods—targeted, semitargeted, and nontargeted. How do the methods differ, and when should they be used?

In general, data acquisition with HRMS is nontargeted. Full-scan MS$^1$ data are almost always collected and will detect with accurate mass measurement any compound from the sample that is ionized and reaches the detector. Collection of MS$^2$ data can also be performed in a nontargeted manner by generating fragment ions from all precursor ions. Alternatively, MS$^2$ data can be collected in a more targeted way with a hybrid quadrupole-HRMS system by only allowing specified precursor ions of interest into a high-energy collision cell to generate product ion spectra.

Postacquisition data analysis can also be performed using targeted, semitargeted, or nontargeted methods. For routine analyses, the most targeted approach to evaluating HRMS data for residues is to generate ion chromatograms for the precursor ions, usually protonated molecules, with a narrow mass extraction window and then to compare these results to a short list of likely analytes or target compounds. In contrast, “semitargeted” screening methods would search HRMS data against a larger database including compounds for which standards may not be available to the analyst. The HRMS results are also always available to review retrospectively for completely nontargeted or unknown compounds. However, because of the time required to examine the data for a large number of additional compounds, this approach may not be practical for aquacultured samples on a routine basis. Nontargeted data analysis could be very valuable for high-priority fish or...
shellfish samples with potentially adverse, but unknown, contamination. If a new contaminant or residue is discovered, it would be possible to evaluate data from previous samples to determine if the compound was present in them also.

In semitargeted screening with HRMS, because full spectral data are collected, it is possible to retroactively review for nontargeted or unknown compounds. How effective is this approach in practice? Have you seen many examples where previously unidentified compounds have been detected later? If so, what generally prompts the researchers to go back to the data?

Because this technique is relatively new, it is difficult to say how practical it will be to retrospectively examine HRMS data from historic samples on a widespread basis. In one specific example, our colleagues from the California Animal Health and Food Safety (CAHFS) laboratory did use this approach to study contamination of pet treats with an antiviral drug residue. As part of a larger investigation into a potential cause for illnesses associated with pet treats, CAHFS began analyzing various jerky samples made from chicken and duck muscle for a wide variety of toxic chemicals. One of the analyses used was a broad LC–HRMS screen on an orbital-trap platform. After the analysis of these samples was underway, Food and Drug Administration (FDA) toxicologists indicated that several antiviral compounds should be included in the jerky treat investigation. In particular, the antiviral drug amantadine had been reported to have been widely used in the Chinese poultry industry. The laboratory obtained a standard of amantadine and tested it to see if the drug could be detected under the chromatographic conditions used for the LC–HRMS screen; several samples of jerky treats were spiked and analyzed to demonstrate that amantadine was recoverable from the jerky. Retention time and exact mass data were then used to retrospectively review data from previously analyzed jerky treats to determine whether this compound was potentially present in the samples. A number of these jerky samples showed a peak with the correct accurate mass for precursor and product ions and retention time match for amantadine. Our laboratory then worked with the CAHFS scientists to validate methods for amantadine and other antiviral compounds that are currently being used to monitor regulatory samples of jerky and other chicken-based pet treats (2).

**Does HRMS have a capability to detect metabolites that triple-quadrupole or ion-trap methods do not?**

All LC–MS instruments can potentially detect any metabolite or compound depending on how the data acquisition is performed. If a triple-quadrupole or ion-trap instrument is being used with targeted data acquisition (via preselected ion transitions or MS^n scan events), then
the metabolite would need to be known and included as part of the method. These instruments, particularly ion-trap systems, could also detect unknown metabolites if operated in a nontargeted data acquisition mode. The advantages of HRMS are that nontargeted acquisition is commonly used and the resulting accurate mass measurements facilitate formula and structural elucidation of unknown metabolites.

Have nontargeted methods been used successfully to detect veterinary drug residues in fish or shellfish?

HRMS screening methods have been shown to successfully detect both targeted and nontargeted veterinary drug residues in fish and shellfish (3–5). The identification of metabolites is an example of being able to detect new analytes using HRMS. Metabolites that we have been able to detect and identify include N4-acetyl sulfonamides in milk and fish, desethylene enrofloxacin in milk and fish, and ethoxyquin dimer in fish. The detection of these metabolites provided verification that the veterinary drugs were administered to the animals and that the residues found were not an artifact of postproduction processing or analysis. Using semitargeted data analysis to look for more veterinary drugs (beyond the compounds listed in the regulatory compliance program), we have found additional residues in eel and frog legs including sulfonamides, and low levels of lincomycin, oxytetracycline, and thiabendazole. The identification of unexpected drug residues in these samples, even at low levels, demonstrated the potential for expanding the scope of monitoring for chemical contaminants in aquacultured products using HRMS screening methods.

In another example of truly nontargeted analysis, HRMS data collected using a single-stage orbital trap instrument and analyzed using differential analysis software was used to identify glycoalkaloid contaminants in dog food (6).

You developed a method for LC–quadrupole time-of-flight (QTOF)-MS analysis of fluoroquinolone antibiotics in aquacultured frog legs (3). First, why did you decide to analyze contaminants in frog legs specifically? Is the volume of frog legs consumed very high?

According to a 2011 report, the international trade in frog legs is a $40-million-per-year business. Most of the product originates in Asian countries, and approximately 2280 metric tons are imported into the United States each year. Frogs are susceptible to many types of bacterial and fungal infections, and contamination of frog legs with Salmonella is a significant problem. An issue of concern related to microbial contamination in food is the use of antibiotics to stem the growth of bacteria. Because the farming of frogs for food is an industry that is not well controlled, it
is important to have sensitive analytical methods to screen, quantify, and confirm the identity of a wide variety of veterinary drug residues, including fluoroquinolones, which might be present in frog leg samples.

What were the advantages of using a hybrid QTOF detector for this analysis? How significant a problem was matrix interference, and how did you address it?

A hybrid QTOF instrument has the advantage of being able to filter specific MS1 precursor ions into a collision cell to form fragments and collect exact-mass data for both precursor and product ions. Including product ions allows for better characterization of any given analyte and is required for confirmation of identity by the FDA (7).

Matrix interference is always a concern with any LC–MS method because ion suppression occurring in an electrospray source can affect quantification. In addition to influencing compound ionization, matrix components may also adversely affect the quality of mass accuracy measurements using HRMS. Coeluted matrix components that are very close in mass-to-charge ratio to the analyte of interest (or to a mass calibration standard) can cause significant shifts in the measured exact mass. The signal from interfering matrix components can be minimized by diluting the sample if there is still adequate sensitivity to detect the analytes of interest. This becomes less of a concern with instruments that have higher resolving power, such as orbital-trap and newer generation TOF instruments, to separate and accurately measure these ions.

How applicable is this method to the analysis of other aquacultured species? The method for frog legs developed using the QTOF system was also tested with other aquacultured species and found to be applicable to catfish, tilapia, and shrimp.

Currently our laboratory is working on an updated HRMS screening method for aquaculture with a hybrid quadrupole orbital-trap LC–HRMS instrument and a generic extraction method using new solid-phase extraction products (5). With this new method, the extraction procedure and MS acquisition parameters were optimized and validated for 60 test compounds representing a variety of veterinary drug classes likely to be used in aquaculture. Semiquantitative data analysis compared MS1 signals for the test compounds to a one-point extracted matrix standard at a target testing level. The test compounds were detected and confirmed in salmon, tilapia, catfish, shrimp, and eel. Because nontargeted HRMS data acquisition was used, the method can also be expanded to monitor for several hundred additional veterinary drugs based on exact mass measurements and retention times. This method is now being used to analyze fish dosed with selected drugs and
aquaculture samples previously found to contain residues.

Your laboratory developed HRMS methods to screen for veterinary drug residues in milk, but faced some challenges when transferring these methods to routine regulatory screening (8). What were those challenges and how did you address them? How effective was your method at detecting the various types of compounds that you wished to detect? What were the limits of detection (LODs)?

The challenges with transferring HRMS screening methods to a routine regulatory laboratory environment mostly involve data analysis. The nontargeted data acquisition of HRMS allows for, in theory, an unlimited number of analytes in milk to be detected. In practice, however, it was not feasible to use this method routinely for samples using a completely nontargeted approach. Although instrument software programs are continually improving their ability to evaluate the large amounts of information generated by HRMS, it can still be difficult to choose data analysis method parameters to adequately capture residue levels of contaminants without producing a large hit list that must be carefully investigated for false positives. Having experimental retention time and product ion information for analytes, in addition to accurate mass measurement of the precursor ion, greatly facilitates the ability to determine if residues found by the HRMS software are really present or just false detects. For example, results from milk sample extracts were evaluated against the veterinary drug database containing several hundred compounds with and without retention time matching. When retention time matching was included, significantly fewer compounds (average of 3) were detected as compared to when only measured exact mass was used (average of 30 compounds “found” in each data file).

Using this method, the screening levels of detection for over 150 veterinary drug residues in milk were determined with LC–QTOF-MS, and over half of those tested could be detected at concentrations of 10 ng/mL or less; 72% were found in milk when fortified at 100 ng/mL. In general, compounds with medium polarity performed well. For example, fluoroquinolones, quinolones, macrolides, lincomycins, many sulfonamides, and some β-lactams could be reliably detected in milk samples at low (≤10 ng/mL) levels. On the other hand, some analytes were only detected at very high fortification levels, or not at all. One reason for this was simply that the analytes did not respond (ionize) very well and their levels of detection, even for solvent standards, were quite high. Another reason why analytes may not have been detected in fortified milk samples was that they were not extracted or recovered from the milk matrix with this procedure.
You also then catalogued a database of product ions for the compounds in question. What is the significance of those data?

Exact-mass data were collected for a large number of compounds using HRMS so that elemental compositions and structures for product ions could be proposed using a combination of measured exact masses, isotope patterns, predictive fragmentation pathways, and published literature. The compiled data can be used for the development of future veterinary drug residue methods regardless of the MS platform (for example, TOF, orbital trap, or triple quadrupole) that is used.

References
ADVANCING THE ANALYSIS OF CONTAMINANTS IN DIETARY SUPPLEMENTS
An Interview with Alexander J. Krynitsky

The size of the dietary supplement market has been expanding significantly in recent years. Given that these products are not regulated, many concerns arise about contaminants that may be present in them, as a result of error or intentional adulteration. Alexander J. Krynitsky, PhD, formerly with the U.S. Food and Drug Administration and currently the director of the Chemical Residues–Food Safety Laboratory at Symbiotic Research, in Mount Olive, New Jersey, has done extensive work to develop effective methods to analyze contaminants in dietary supplements. He recently spoke to us about this work, including a method he has developed to quantify 96 contaminants in a range of matrices.

One of the areas you have worked on has been the analysis of contaminants—both intentional and unintentional—in dietary supplements. How widespread and serious is this problem? Do we have any way of knowing what percentage of products on the market contain such contaminants?

Both intentional and unintentional adulteration of dietary supplements is pretty widespread; given that there has been an increase in use of dietary supplements over the years, there is an increased chance for these products to be economically adulterated. I cannot put a number on the percentages because it depends on the product (such as supplements for weight loss, body building, and sexual-performance enhancement).

You developed a method for simultaneous quantification of 96 contaminants in herbal dietary supplements, including a wide range of pharmaceuticals, plant toxins, and some secondary metabolites (1). When you were developing this method, how did you approach the problem of having such a wide range of target analytes and matrices?

We took a very general approach with
PESTICIDE RESIDUES  VETERINARY DRUG RESIDUES  CONTAMINANTS IN DIETARY SUPPLEMENTS  ENSURING ACCURACY

regard to extraction and cleanup. We did not want to use too specific of a cleanup approach because we did not want to lose analytes—which was a risk given that we were dealing with many compounds with a wide range of polarities. The approach we took was using the QuEChERS (quick, easy, cheap, effective, rugged, and safe) sample preparation procedure that has been used worldwide in the analysis of pesticides and other small-molecule contaminants. For the determinative step, we used a generic reversed-phase ultrahigh-pressure liquid chromatography (UHPLC) gradient, interfaced to quadrupole-orbital ion trap mass spectrometry.

Given the range of matrices involved, how important a role does sample preparation play in this method, and how did you optimize it for the challenge at hand? The QuEChERS protocol adopted in this study enabled effective extraction of most of the analytes from the evaluated matrices. Expectedly, low recoveries were obtained for highly polar analytes (such as metformin, tropine, and ouabain). Given the high affinity of these compounds for the aqueous phase, they could not be completely transferred into the acetonitrile layer during salt-induced phase separation. The pH of the examined matrices influenced the extraction efficiency for some basic analytes, such as pyrrolizidine alkaloids and their N-oxides or 1,3-dimethylamylamine. In the case of acidic matrices (for which the pH of the aqueous extract was <4.5), good recoveries were obtained, but the extraction of those with pH values >5 did not provide acceptable results. The recoveries of problematic analytes significantly improved when 2% formic acid was added to the aqueous or organic components of the extraction mixture. The extraction at the lower pH probably prevented or at least minimized the binding of the analytes to the sample matrix through interactions between their charged functional groups. The defatting by hexane and the dispersive solid-phase extraction (dSPE) using C18 sorbent were shown to be effective only in the cleanup of oily matrices (softgels), as it enabled the removal of some nonpolar coextracts and slightly decreased the matrix effects while not decreasing recoveries of analytes. This result was not observed for other test matrices.

How did you optimize the UHPLC separation in the method to address the range of analytes? The optimization of chromatographic separation was performed with methanol and acetonitrile solvent standards and matrix-matched standards prepared in acetonitrile. The combined use of the UPLC HSS T3 column (Waters Corporation) and gradient elution with mobile-phase components containing formic acid and ammonium formate as additives allowed separation of the
analytes within 11 min with typical baseline peak widths ranging from 5 to 12 s. Good within- and between-measurement sequence retention time stability ranging from 0.15% to 3.5% (RSD) was achieved for all analyte–matrix combinations. It is noteworthy that higher RSDs were obtained for analytes that were eluted early in the chromatographic run. The endcapped stationary phase provided improved retention for highly polar analytes, such as metformin and tropine (with retention factor values of 0.7), which would not be retained by conventional reversed-phase sorbents. A decrease in the injection volume from 3 to 1 μL resulted in significant improvement of peak shapes of problematic compounds.

To compensate for sample-to-sample variation in matrix effects, how did you choose between the method of standard additions or dilution of extracts?

Considering the variation of matrix effects that occurs during electrospray ionization (ESI) of extracts obtained from different types of herbal dietary supplements, use of matrix-matched calibration is not a reasonable option for use in quantifying analyte concentrations in a wide range of commercial samples. There are several alternative strategies for overcoming problems with quantification caused by the matrix effects. In this study, we investigated the applicability of the method of standard additions and elimination of matrix effects by dilution of sample extracts and quantification using solvent standards. For most of the analyte–matrix combinations, the recovery values and precision values achieved by this quantification approach were in good agreement with those obtained using matrix-matched standards. These results confirm that the method of standard additions effectively compensates for matrix-induced signal suppression or enhancement of analyte signals and is fit-for-purpose in this application.

The drawback of this approach is that it is time-consuming and laborious, as it requires preparation and analysis of multiple postextraction spikes for each of the examined samples. Extract dilution, on the other hand, represents a straightforward procedure leading to reduction of coextracted compounds, and thus a reduction in the extent of matrix effects. Depending on the test matrix, the reduction of matrix effects below ±20% was achieved for 44–71% of target compounds that had initial signal suppression or enhancement above this value at the spiking concentration of 500 μg/kg. The corresponding percentage of analytes at 50 μg/kg was lower and ranged from 11% to 40%, as the use of dilution resulted in an increase of limits of detection (LODs) and limits of quantitation (LOQs). For the majority of compounds with signal suppression >20%, a dilution factor of 25 or higher (up to as much as 10,000) had to be used.
Under these conditions the complete elimination of matrix effects is possible, without compromising the detectability of analytes. The recoveries calculated by this quantification approach ranged from 82% to 98%.

How did you optimize the normalized collision energy (NCE) values for the quadrupole–orbital ion trap MS step of this method? Despite the fact that this mass spectrometer uses the principle of NCE, which compensates for mass dependency of the optimal CE, initial experiments have clearly shown that neither a single generic NCE setting nor the three-step fragmentation at varying NCE (so called “stepped NCE”) can be used to obtain acceptable results for all of the analytes. Therefore, optimization of collision energy was performed for each of the target analytes to achieve adequate responses of product ions.

How did you determine the best mass resolving power and scan speed? The use of 70,000/35,000 full width at half maximum (FWHM) represents a compromise between spectral resolution and scan speed and this setting was used for measurements in this study. Excellent mass accuracy with typical mass errors of ±3.0 ppm was achieved in full MS mode for all analytes and test matrix combinations.

How much faster was your UHPLC–MS method for this analysis than previously published high performance liquid chromatography (HPLC)–MS methods? Our UHPLC-MS method is about 20–30 min faster per chromatographic run.

What unexpected compounds or concentrations of expected compounds did you find in the 23 dietary supplements you obtained from the retail market and tested? In the final phase of the study, the developed method was applied to the examination of 23 dietary supplements obtained from the retail market. The most frequently detected analytes were the coumarin compounds scopoletin, umbelliferone, and bergapten, occurring at concentrations ranging from 35–4203 μg/kg.

The synthetic drug sibutramine was detected in two supplements claiming weight-loss effects at 3348 and 48,150 μg/kg, respectively. These concentrations are well below those corresponding to therapeutic doses of sibutramine. Therefore, the presence of this pharmaceutical may represent cross-contamination during production of the supplement. The presence of the aphrodisiacs icariin and yohimbine in supplements for male performance enhancement was in good agreement with information provided on the product labels.

You have used both low-resolution and
high-resolution mass spectrometry (HRMS) in the analysis of contaminants in botanical dietary supplements. What do you see as the ideal role for each?
Low-resolution LC–MS-MS can be used for routine targeted screening of these compounds in a laboratory situation where HRMS is not available. HRMS can be used for identifying unknowns and newer active pharmaceutical ingredients.

What further work remains to be done in the analysis of dietary supplements?
We need to develop targeted screening approaches for these compounds using low-resolution LC–MS-MS for routine analysis to benefit the laboratories that do not have HRMS or that only have limited access to it.

References

Safeguarding the global food supply requires continuous, accurate and timely monitoring of harmful compounds. Quantify more chemical residues, at lower levels, while meeting global regulatory demands with our new portfolio of LC-MS instruments, sample prep solutions and software. Triple quadrupole MS delivers SRM sensitivity and speed to detect targeted compounds more quickly and HRAM solutions using Thermo Scientific™ Orbitrap™ MS enables screening with accurate quantitation of hundreds of contaminants. Meet today’s challenges with us and together, we’ll transform quantitative food safety analysis.

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Analytical chemists working in the analysis of pesticides and other chemical residues in food regularly deal with many challenges, such as complex matrices, ever-changing contaminants, demands for high throughput, and questions of obtaining a representative sample. Steven J. Lehotay, PhD, of the United States Department of Agriculture’s Agricultural Research Service, famous for co-inventing the QuEChERS sample preparation method in 2002, has a passion for improving the work food analysts do. Here, he talks about work practices and approaches that food analysts need to consider to ensure excellent results in what are often challenging conditions.

In a paper last year, you wrote that sampling and sample processing have been too often neglected in pesticide residue analysis (1). Do you think common practice is poor today? No, not “poor,” but not as good as desirable or possible. The results presented in Figure 1 (1) show that the differences in results from reanalyses of duplicate sample portions after sample processing by common practices average <20%. Some analytes and matrices can be problematic, and some outliers are listed in the figure. The overall quality of results surpasses or matches what is commonly achieved by labs participating in proficiency test samples using well-characterized samples. However, there is no doubt that the devices and protocols used for sample comminution should be improved. The 10–15 g sample size used in the QuEChERS (quick, easy, cheap, effective, rugged, and safe) method requires better performance and more care in the sample chopping step than methods using larger test portions, especially now as chemists are beginning to reduce analytical test portions even smaller in “mini-QuEChERS.”

In my view, a quality control (QC) standard (a relatively stable and easily detected chemical that will not appear in
real samples) should be added to the bulk samples as they are being comminuted. The consistency of the sample processing step can then be assessed by comparing results with other processed samples over time. This step alone will probably improve results because people generally do better work when they know that their performance is being monitored. We analytical chemists cannot hide from our results, and we must face up to facts and find solutions. Our very jobs require us to be meticulous and good problem solvers. Also, personal accountability, responsibility, and a competitive spirit will lead to improved performance over time, just as has been shown previously in proficiency testing trends.

What are the smallest dry and wet samples that can produce accurate test results for pesticide residue analysis in foods? How do we ensure that samples, which may be less than 15 g for a food commodity of greater than 1 kg, are truly representative? Dry commodities are generally easier to comminute, and standard milling can make fine powders like flour, permitting 1-g test portions, or even less, to yield accurate and representative results. With respect to high-moisture foods, some studies of subsample sizes of different analytes in different food commodities have been reported, but what is acceptable depends on several factors. Some analytes and matrices

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Figure 1: Difference in results versus mean concentrations in reanalyses of 15–50 g duplicate test samples that were subsampled from ~1-kg samples comminuted at room temperature and stored frozen until confirmatory reanalysis of potentially violative samples on a different date. (Reprinted with permission from reference 1.)
need more time and effort than others. Certainly, 25–30 g test portions of fruits and vegetables comminuted in standard choppers have been shown to yield similar quality of results as analyses of 50–100 g test portions. However, dry ice or other means of cryogenic-based comminution of frozen samples has been shown to yield equivalent or better data quality for 10 g or even smaller subsamples, with the added benefit of reducing analyte degradation or volatilization, or both. Precautions should be made when using cryogenics to avoid excessive condensation of moisture from the air, but the QC standard approach that I recommended in my answer to the previous question could account for this potential bias.

In a broader perspective, we all must consider if the analytical result achieves its intended purpose. Legislation, policies, and well-established sample collection protocols address the issue of bulk sample collection. Periodic evaluations of sample collection by analyzing duplicate bulk portions should be done to compare consistency of results. Of course, inaccuracies will occur in specific instances, which is the nature of statistics, but overall, samples collected using current standard operating procedures (SOPs) meet needs for the analysis. In any case, the sample provided to the lab by default becomes the sample of record. In confirmatory analyses and disputes, another subsample of the stored comminuted sample is typically taken as the test portion, not the original bulk sample. This need for consistency emphasizes the importance of following SOPs and recording information for chain-of-custody records.

Can accurate sampling be achieved with automated systems, which typically use small sample sizes? We and others are investigating this very issue, and I look forward to being able to better answer this question in a few years.

You recently conducted a study to investigate variables affecting QuEChERS-based extraction yields of incurred (that is, not spiked) pesticides and environmental contaminants in fish samples (2). What did you find in terms of efficiencies achieved using various extraction devices and extraction times? I invite readers to review that paper because it shows that in the case of well-comminuted fish, a 2-g test portion extracted by mechanical shaking in QuEChERS for 10 min statistically achieved the same results for many incurred analytes as larger sample sizes extracted by a more vigorous method with a probe blender. The platform vortex shaker used could extract 50 samples at a time, or even more depending on the size of tubes that are used. Figure 2, which shows the accuracy of measurements of polybrominated diphenyl ethers (PBDEs) in National Institute of Standards and Technology (NIST) standard reference...
material (SRM) 1947 (Lake Michigan fish tissue), demonstrates that even a 1-min shaking time with acetonitrile yields equivalent results very near the certified concentration as extensive extraction by blending.

Another aspect of method accuracy that you have been investigating relates to the practice of chromatographic peak integration. Do you think that chromatographers obtain consistent areas in peak integration? What do you recommend as a best practice?

I have conducted chromatography since 1985 on countless instruments, and in all that time, I have yet to encounter a reliable and accurate automated peak integration software tool that can be trusted without careful human review. Especially at low analyte levels, variations in peak shapes and noise (electronic and chemical) render nearly any sophisticated software program less reliable than human judgment. In the past, when we determined only a small number of analytes in a small number of samples that took days to prepare, manually integrating peaks was not an onerous task. However, modern methods include hundreds of analytes in the chromatograms, and the sample preparation and analysis methods are so fast and easy that scores of samples
can be run in a single batch. Correct peak integration is fundamental to data integrity and quality, but like sample processing, it is not given the attention it deserves. As much as I like to listen to music when I spend many hours reviewing chromatographic peak integrations, data review is a very time-consuming task that has become the rate-limiting step in overall sample throughput in many labs. All practicing chromatographers experience this kind of mind-numbing tediousness, and they also realize the importance of staying sharp during data review to conduct consistent and proper manual integrations if they want to achieve high-quality results. I can give examples when day-dreaming analysts have caused embarrassment, but it is too much to expect for humans to be perfect.

When we switched from high performance liquid chromatography (HPLC) to ultrahigh-pressure liquid chromatography (UHPLC) about eight years ago in my lab, we noticed that analyte retention times and peak widths, which often varied widely in HPLC, became very consistent in UHPLC. I observed the same thing for gas chromatography (GC)-amenable analytes when we switched to tandem mass spectrometry (MS–MS) in low-pressure GC at about the same time (3). Analyte protectants are also very useful in GC to maintain consistent retention times and peak shapes during long analytical sequences. Last year, we were able to upgrade our GC–MS-MS system to the latest commercial generation, which enabled us to lower our injection volume from 2.5–10 μL using cold programmable temperature vaporization (PTV) to 1 μL or even less in hot split-splitless injection. This still allows us to meet <10-ng/g limit of quantification (LOQ) needs, with the benefit of even more consistent and rugged chromatographic separations.

In the early days of computers, chromatographic peak integration programs were very simple to save time on data processing. I always appreciated the most reliable integration function, which is known by “summation” in some software tools. The operator simply enters the chromatographic start and stop times of the integrator, and it calculates the area of the peak (or noise) between those two times. If the retention time and peak widths are consistent, then the integrations will be reliable. If interferences are present, then any peak integration function will not work ideally, but noise is greatly reduced in highly selective modern MS-based detectors, so this problem is less severe now.

Despite the reduced chemical background noise, common analytes analyzed in rapid methods using generic multiresidue chromatographic conditions often have multiple or misshapen peaks (or both) that aren’t integrated consistently even with the most sophisticated software in MS-based systems. Using “advanced” programs, it is not unusual for “optimized” integration parameters to mis-integrate multiple
injections of the low-level analytes, even in repeated injections of the same extract. However, the good, old fast and easy summation integration function can do the job so reliably that it eliminates the need for human review altogether! Then, automated post-integration “yes/no” decision-making can be done based on three factors. First, does the integrated signal intensity lead to an analyte concentration above the reporting limit (for example, 10 ng/g)? Second, does the apex of the peak (retention time) fall within the acceptable reference peak window for the analyte and its other MS-based peaks (for example, diagnostic ions)? Third, are the integrated peak intensities of the diagnostic ions (or other identification parameters) within the acceptable range of the analyte versus the reference standard? If those conditions are met, then the peak is reported as positive, which eliminates very time-consuming and highly variable subjective human judgment at this step.

Figure 3 provides an example of the ease and consistency of summation integration. Note the excellent reproducibility of retention times and peak widths even after 325 injections over the course of five days in complicated matrix extracts. The LOQs remained ~2 ng/mL throughout the study, and the combined calibration curve had $R^2 = 0.990$ in this example. We’ve shown this automated summation integration and post-run decision-making approach to be more accurate both quantitatively and qualitatively overall than current sophisticated integration programs without human review. A smart and careful analyst can slightly outperform either approach, but it takes a long, concentrated effort that is infeasible in real-world practice. Our approach saves many hours of labor in the lab, and greatly increases lab efficiency and sample throughput.

In another recent paper, you discussed issues involving accuracy in the screening and identification of chemical contaminants in food by mass spectrometry (4). One of the concerns you raised was related to careless use of terms such as indication, determination, identification, confirmation, sensitivity, and detectability. What are the correct uses of those terms? Frequent participants of the North American Chemical Residue Workshop (NACRW) may tire of hearing me point out when speakers misuse these terms, but at least they should know the distinctions in terminology. Indication means a positive result from a screening test; determination relates to the quantitative result; identification should be used when discussing the result from a single MS-based analysis in which predefined criteria have been met; and confirmation entails the results from two analyses in agreement (usually involving both determination and identification). Regulatory enforcement actions should always require confirmation of a duplicate
test portion (not of the same extract), preferably using methods with different chemical mechanisms. Another common error by many analytical chemists is to equate high sensitivity with low detection limit. Sensitivity only relates to detector response relative to the amount of analyte, or slope of a calibration curve. Instrument vendors typically refer to “sensitivity” of their instruments, but they nearly always misuse the term by referring to signal-to-noise ratio (S/N) for easily detected chemicals in solvent solutions. Yes, higher sensitivity is most important when noise levels are constant (or zero), but chemical noise from complicated matrices is often the limiting aspect in achieving low LOQs.

In real-world applications, selectivity is often more important than sensitivity. For example, MS is always more sensitive than MS-MS, but MS-MS nearly always yields lower LOQs by avoiding interferences. For this reason, I (and others) suggest use of the term detectability, which takes into account the degrees of both sensitivity and selectivity.

Figure 3: Use of summation integration in the case of a 1-µL injection in low-pressure GC–MS-MS analysis of 5 ng/mL endosulfan sulfate in 10 different matrices (RO = reagent-only) over the course of five days (325 injections, including 230 matrix extracts) without changing the liner.
Considering all of these questions broadly, what else needs to be done to ensure that food analysts achieve robust, rugged, reliable, and high-throughput analysis, and can do so at an affordable cost?

Proven means of advanced and efficient operations are known and have been implemented in several leading labs, but affordable is a relative term. Expensive instruments are nearly always needed, which requires sufficient expertise, lab infrastructure, maintenance, and a high capital cost at regular intervals. Not all organizations can afford these costs (or don’t prioritize for them), but there comes a point when even experienced chemists using old instruments simply cannot meet current standards for the analytical purpose. Some people like to rationalize inaction by saying “if it ain’t broke, don’t fix it,” but I remind them “if you don’t fix it, you’ll go broke” (or be out of a job).

Even when labs have enough funding and support, decision-makers still need to be knowledgeable enough to implement appropriate techniques, hire skilled analytical chemists, and spend funds wisely. Frankly, more chemists in the residue analysis field need to study the scientific literature and discuss specific details with experts via email and meetings, especially internationally. As an American, it disappoints me to see the USA fall behind other countries in some areas in which we used to lead. At the same time, I am glad to see such rapid improvement from developing countries. I see greater investment, more interest, and often get better questions about chemical analysis from Asia and Latin America than within the USA. International visiting scientists receive grants to come to my lab (and other labs), or to participate in hands-on training courses, but fewer American chemists have that chance or take the initiative. Seeing is believing, and I encourage more chemists to see for themselves different ways of doing things.

Money is not the only factor, though, and more young chemists are joining the workforce. I am pleased by the greater technological skills, enthusiasm, and energy they bring to the field. I have much to learn from them in advanced computer and data management techniques, for example, and I look forward to using new ways to handle the overwhelming amount of data generated in high-throughput analyses.

**What are the next steps in your work?**

Since I joined the US Department of Agriculture’s Agricultural Research Service (USDA-ARS) in 1992, I’ve been striving to develop highly effective and efficient ways to “have our cake and eat it, too” in chemical residue analysis. Technology has come a long way, and we are investigating techniques now that we could only imagine at the start of my career. I am very excited by recent developments, not just in my lab, but also among colleagues, and am unable to keep up with plans. I love to hear
“wow” from visitors, and we’ve been hearing that a lot lately. My partners and I have been as productive as ever, and I invite the reader to look into all of our papers. I think many analytical chemists can particularly benefit from the recent publications cited in this article (1–5).

Figure 4 indicates the sample throughput possible in the recent past, current situation, and near future in chemical residue analysis of foods. Our next step is to optimize, validate, and implement high-throughput start-to-finish protocols for hundreds of veterinary drugs, pesticides, and environmental and emerging contaminants in foods. We would like the methods to be turnkey for different instruments and easily transferred to other labs. I think we are on the verge of achieving this goal using QuEChERS for rapid batch sample extraction followed by automated cleanup (5) and fast (10 min each) analyses by UHPLC and low-pressure GC (3) both coupled to reliable MS-based determinations and identifications without human review. The methods are so rugged that hundreds of sample injections can be made before needing to conduct instrument maintenance. We are also seeking to eliminate the need for matrix-matched calibration standards, which has long been a source of analytical bias and inefficiency in routine lab operations.

In the longer term, we plan to
investigate even faster analyses and attempt to improve sample processing, which has become the rate-limiting step in sample throughput. Labs spend hundreds of thousands of dollars on sophisticated instruments and highly trained operators to conduct the final analytical step, but the overall accuracy of results is often limited by the quality of sample comminution performed by nontechnical personnel typically using inexpensive food choppers. Equipment that can process bulk samples in parallel to yield <10-g representative subsamples would be very valuable to many labs.

References
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