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APGC-MS/MS: A New Gold Standard for Dioxin and Furan Analysis

Joe Romano, Senior Manager, Food and Environmental Global Accounts, Waters Corporation,
Douglas Stevens, Principal Scientist Food and Environmental, Waters Corporation,
and Coreen Hamilton, Senior Scientist, SGS AXYS Analytical Services Ltd.

INTRODUCTION

Polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs) are toxic compounds categorized as persistent organic pollutants (POPs) and are ubiquitous throughout the world. Known as dioxins and dioxin-like substances, they remain in the environment long after initial contamination and their bioaccumulative nature makes their presence in the food chain a considerable risk to human health. PCDDs and PCDFs arise through natural events, such as forest fires and volcanic eruptions, and anthropogenic routes, for example as a by-product of industrial activities including waste incineration, decolorizing of paper pulp, and the manufacturing of some herbicides and pesticides. When emitted into the air, dioxins can deposit locally on plants and on soil, contaminating water sources, food, and feed. Dioxins can also be widely distributed by long-range atmospheric transport, depositing far from the site of release.

Dioxins and furans belong to the group of POPs known as halogenated hydrocarbons, characterized by their low water solubility and high lipid solubility. This lipophilic nature results in the tendency for dioxins and furans to preferentially dissolve in fats and lipids, rather than water, which leads to the bioconcentration of these contaminants in tissue and its accumulation in the food chain. This lipophilicity also enables these POPs to pass more easily through the phospholipid layer of biological membranes, increasing their ability to accumulate in fat.

More than 90% of human exposure to dioxins is through the food supply, primarily meat and dairy products, fish, and shellfish. Protecting the food supply and preventing secondary contamination through the food chain is therefore critical. Good controls and practices during primary production, processing, distribution, and sale are all essential in the production of safe food. Studies into the short- and long-term health effects of dioxins are ongoing. For example, in 2001 the Joint Food and Agriculture Organization of the United Nations (FAO)/WHO Expert Committee on Food Additives (JECFA) performed an updated comprehensive risk assessment of PCDDs, PCDFs, and "dioxin-like" PCBs. Additionally, the WHO established a 'Code of Practice for the Prevention and Reduction of Dioxin and Dioxin-like PCB Contamination in Foods and Feed' in collaboration with the FAO, providing guidance to national and regional authorities on preventive measures.[1]

The synthesis of dioxins and furans was first documented by German scientists in 1872, who intentionally prepared an octachlorinated compound,[2] but it was not until the late 1950s that the structure of these compounds was investigated and elucidated.[3] Dioxins are a by-product of the synthesis of some pesticides such as 2,4-D and 2,4,5-T, which have historically seen widespread use around the world.

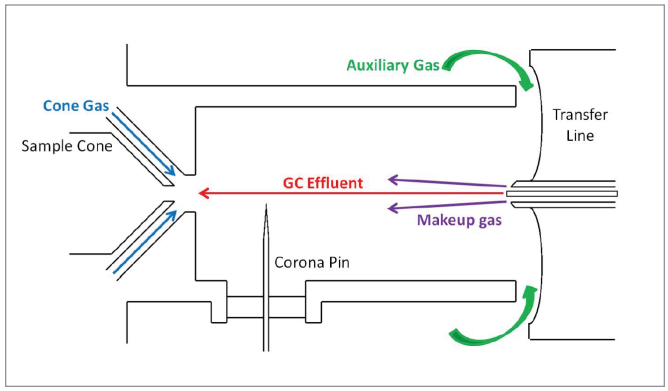
The hazardous effects of dioxins and dioxin-like substances to living organisms are well documented and have been linked to a variety of conditions including type 2 diabetes, ischemic heart disease, and an acne-like skin disease called chloracne, which is a hallmark of dioxin exposure. The most toxic dioxin compound, 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD), is classified as a Group 1 carcinogen by the World Health Organization's (WHO) International Agency for Research on Cancer (IARC).[4] Dioxins are two- or three-ring structures that can be chlorinated to varying degrees: PCDDs and PCDFs can have up to eight. Mixtures of the substances with different numbers and positions of chlorine substitution are found in the environment, and the degree of chlorination of dioxin mixtures released to the environment through incineration is determined by the source material and the amount of chlorine available.

Up to eight chlorine atoms can be placed on the basic structure of dioxins and furans, giving rise to 75 and 135 congeners, respectively. While not all congeners are considered toxic, the separation of these interfering compounds from their toxic counterparts is vital for environmental risk and health assessments.

Detecting trace levels of PCDD and PCDF is important to monitor food supplies, to ensure industrial emissions meet regulatory standards, to track sources of ongoing emissions, to identify contaminated sites, to inform risk assessments, and to contribute to human health assessment by measuring body burdens. Analysis requires highly sophisticated, sensitive analytical systems that are currently available only in a limited number of laboratories around the world. The analysis costs are very high and vary according to the type of sample, but range from over US $1,000 for the analysis of a single biological sample to several thousand US dollars for the comprehensive assessment of release from a waste incinerator.[5]

THE EVOLUTION OF DETECTION TECHNOLOGY

Prior to the 1970s, detection of dioxins was primarily obtained using packed-column gas chromatography (GC) with electron capture detection (ECD) in the parts-per-million (ppm) and parts-per-billion (ppb) range.[6] However, problems with specificity and detection limits, resulting from the technique's inability to process highly complex environmental samples, spurred the development of gas chromatography mass spectrometry (GC-MS) methods between the 1970s–80s. Although GC-MS showed improvements and allowed many different samples types to be analyzed in order to determine the environmental distribution of dioxins, this method alone was insufficient and required intensive front-end chemistry to separate trace analytes from potential interferences.



Schematic of APGC chamber showing gas flows.

Conventional mass spectrometry (MS) detection was not suitable, as electron ionization (EI) mass spectra of some dioxin and furan isomers are almost identical. Other methods such as Fourier transform infrared (FT-IR) and nuclear magnetic resonance (NMR) spectroscopy do not have sufficient sensitivity for detection at biologically relevant levels. Furthermore, during this period advances in both high performance liquid chromatography (HPLC) and high resolution capillary GC (HRGC) were applied to the separation of dioxin isomers. These developments were among some of the early steps aimed at enabling routine dioxin measurements to be conducted by relatively inexperienced analysts.

In the early days of highly specific and sensitive dioxin analytical methods, EI GC-MS on a magnetic sector mass spectrometer was the key technology used for highly precise, accurate, high confidence quantitative environmental analysis, cementing its use for dioxin monitoring. Despite the benefits of high resolution, magnetic sector instruments require a high degree of expertise and are expensive, limiting their widespread use.

Following the 1999 dioxin crisis in Belgium[7] and the Stockholm Convention for POPs in 2001, the European Commission implemented an official continuous control strategy for food and feed. At the time, no standardized methods for food were available, but GC coupled with (magnetic sector) high resolution mass spectrometry (GC-HRMS) was widely accepted as the most sensitive and selective tool, especially in comparison with other MS analyzers such as time-of-flight (TOF).[8] The current US Environmental Protection Agency (EPA) guidance therefore recognizes HRGC/HRMS as the 'gold standard' for dioxin and furan detection in aqueous, solid, and tissue matrices, under the EPA Method 1613B.[9] This method analyzes PCDDs and PCDFs in the picogram per liter (pg/L) range, and its high resolution capabilities enable masses to be differentiated to the 4th decimal place.

However, in the intervening years between the 1970s and the 1990s, tandem quadrupole MS, also known as MS/MS, gradually rose in popularity for a variety of quantitative applications. Here, two low resolution (1 atomic mass unit) mass spectrometers are assembled in tandem with a collision cell in between, limiting the need to employ high mass resolution and therefore saving costs, while maintaining the specificity and sensitivity of methods such as HRMS. Recent technical developments in GC-MS/MS using triple quadrupole analyzers have spurred the revision of European Commission specific criteria and US EPA interest, to recognize the performance similarities of this method with GC-HRMS.

In addition to mass analyzer development, the range of types of ionization have evolved and progressed, particularly in the atmospheric region. Atmospheric pressure chemical ionization (APCI) sources with MS/MS offer a number of advantages over EI on a magnetic sector, including the capability for targeted analysis and very low detection of target analytes in complex samples. Additionally, EI is a hard ionization source, and extensive fragmentation associated with this technique can impact the abundance of the molecular ion and compound specific spectra. APCI is a softer technique, where the molecule is ionized by either proton transfer or charge transfer, rather than by direct electron bombardment, thus providing a more abundant molecular ion. Because the molecular ion is the single most specific spectral peak for any given analyte, a high absolute and relative abundance molecular ion matched with a defined extent of fragmentation to a specific fragment ion yields both high sensitivity and high specificity.

ALTERNATIVE METHOD DEVELOPMENT

In 2014, the European Union (EU) passed legislation recognizing the use of triple quadrupole GC-MS/MS, with either EI or APCI, as a confirmatory tool for checking compliance with maximum levels of dioxins in food and feed (589/2014/EU[10] and 709/2014[11]). This was the result of an extensive validation study by an EU working group, and was the first official regulatory method that began the switch from magnetic sector technology and included APCI.

The WHO conducted human-based risk assessments, setting Toxic Equivalency Factors (TEFs) for dioxins,[12] and the results of analysis of these compounds in samples should be reported as lower bound, medium bound and upper bound concentration, by multiplying each congener by their respective TEF and summing them to provide the total concentration, expressed as Toxic Equivalency (TEQ). This system was developed to facilitate risk assessment and regulatory control of dioxins, furans, and PCBs.

In line with the ongoing innovation in dioxin analysis technology, the US EPA is currently evaluating a new method – atmospheric pressure gas chromatography tandem mass spectrometry (APGC-MS/MS) – in collaboration with SGS AXYS and Waters Corporation to develop and validate an alternative procedure for PCDD/PCDF analysis using MS/MS rather than HRMS. This method has already demonstrated to be a robust and sensitive option for confirmatory analysis of PCDDs and PCDFs, in compliance with 589/2014/EU.[13] The project aims to adapt Method 1613B protocols and criteria to MS/MS, showing equivalency of results in terms of sensitivity, linearity, selectivity, accuracy, and precision.

Approval of a new method that uses GC-MS/MS for determining dioxins would take advantage of the technological advances made in tandem quadrupole MS over the decades, and also has the potential to lower laboratory costs.

The first objective of the study was to set up a GC-MS/MS method that includes all the acquisition protocols and quality control (QC) checks appropriate for an MS/MS method, and to investigate the effect of any potential interferences such as chlorinated diphenyl ethers (CDPEs), PCBs, pesticides, and polyaromatic hydrocarbons (PAHs). Interference from CDPEs must be monitored during the analysis of PCDFs under EPA Method 1613B, as the loss of two chlorines from a CDPE occurs readily, resulting in fragment ions with a mass-to-charge ratio (*m/z*) equal to the corresponding PCDF *m/z*. This requirement for monitoring CDPE, as well as the performance of additional extract cleanup, was maintained in the MS/MS method. The interference from PCBs was also considered, as high concentrations of PCBs from higher levels of chlorination in extracts can give responses in PCDD/PCDF channels. The impact was determined as minor, but it is recommended that extract clean-up procedures include a step known to remove PCBs and if they are not removed, to monitor MRM transitions for PCBs to detect them. This additional clean-up to remove interfering PCBs was adapted from existing EI magnetic sector methods, which can also encounter this problem.

The second objective was to demonstrate the ability of GC-MS/MS to achieve all performance specifications in Method 1613B, including sensitivity, linearity, selectivity, accuracy, and precision. Using the finalized MS/MS acquisition method with all built in QC checks in step one, samples were run that had previously been analyzed by GC-HRMS according to Method 1613B, to enable direct comparison of results. Method detection limit (MDL) studies from three matrices (aqueous, solids, and tissues) were run on each system and compared to minimum levels (MLs) in Method 1613B.

To test robustness, nine real world samples from four matrices (aqueous, solids, biosolids, and tissues) were run on MS/MS and compared to HRMS.

VALIDATION OF THE METHOD

The GC-MS/MS method was developed and validated (Tier 3 validation) using the Waters™ APGC™-Xevo™ TQ-XS, which uses atmospheric pressure chemical ionization with nitrogen gas. The atmospheric pressure source results in less fragmentation and therefore more sensitivity and selectivity than an EI source. The Xevo TQ-XS tandem quadrupole mass spectrometer is a high performance system optimized for high sensitivity and specificity, combined with a wide linear dynamic range even at high acquisition rates.

All data for the PCDD/PCDF method were acquired by operating the MS/MS system in the multiple reaction monitoring (MRM) mode. The first mass analyzer (MS1) is set to select ions of a particular *m/z*, known as precursor ions. These precursor ions are transmitted to the collision cell where they undergo collision-induced dissociation using a neutral gas (argon) to produce an array of fragment ions (product ions). The product ions with high ion intensity and characteristics of the analyte are selectively transmitted to the second mass analyzer (MS2), where they are sorted according to their *m/z* values. In the MRM mode, only the selected product ion reaches the detector and the detected signals are recorded as an ion chromatogram for the precursor-product ion transition. MRM therefore delivers a unique product ion that can be monitored and quantified in a highly complicated matrix, providing the selectivity required for PCDD/PCDF analysis.

The nature of MS/MS results in minimal noise reaching the detector, leading to good signal-to-noise (S/N) even for trace level analysis. To demonstrate the sensitivity and linearity of APGC-MS/MS, in line with EPA Method 1613B requirements (at least 10:1 S/N for the CS1 calibration standard), an example chromatogram for 2,3,7,8-TCDD in a CS0.2 standard (one-fifth the concentration of CS1 or 0.1 ng/mL) is shown in Figure 1.

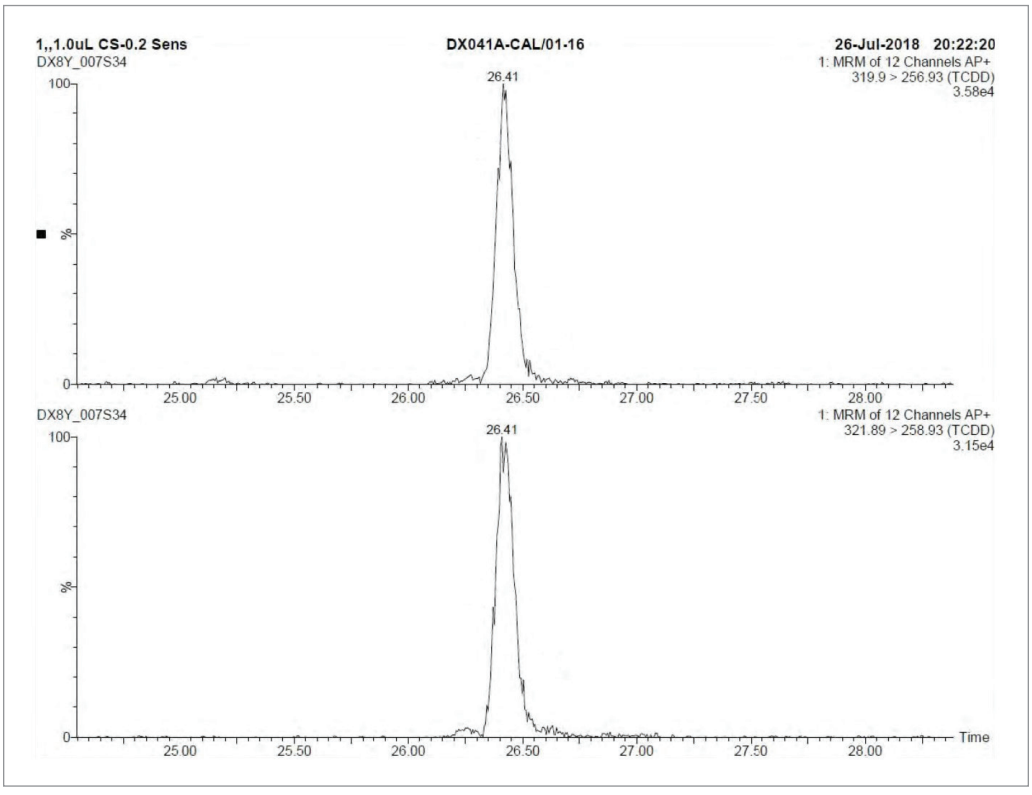


Figure 1. Multiple reaction monitoring (MRM) response of 2,3,7,8-TCDD for 0.1 pg injection (unsmoothed data).

It was important that, as well as establishing operating protocols for APGC-MS/MS to analyze PCDD/PCDFs and meeting the quality assurance/quality control (QA/QC) specifications of Method 1613B, the new method could produce accurate data for real world samples with complex sample matrices. Nine different samples of four matrices – wastewater, biosolid, sediment, and tissue – were analyzed, and comparison of HRMS and MS/MS for all 36 samples showed excellent agreement (Figures 2–5).

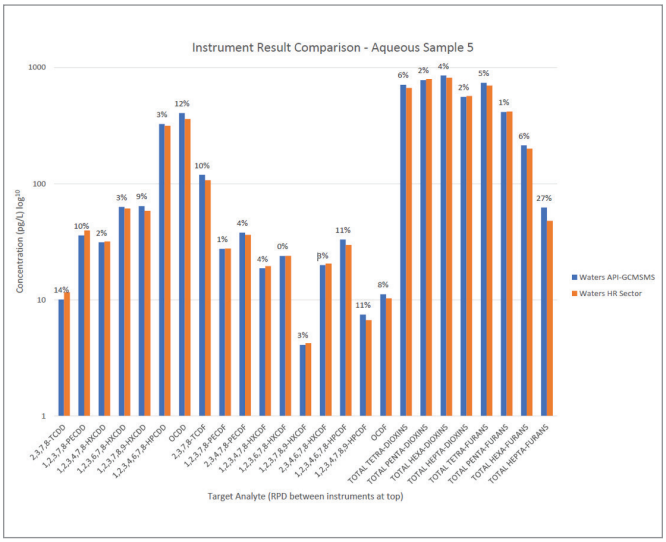


Figure 2. Wastewater sample. Tandem quadrupole (MS/MS) compared with high resolution mass spectrometry (HRMS). RPD = Relative percent difference.

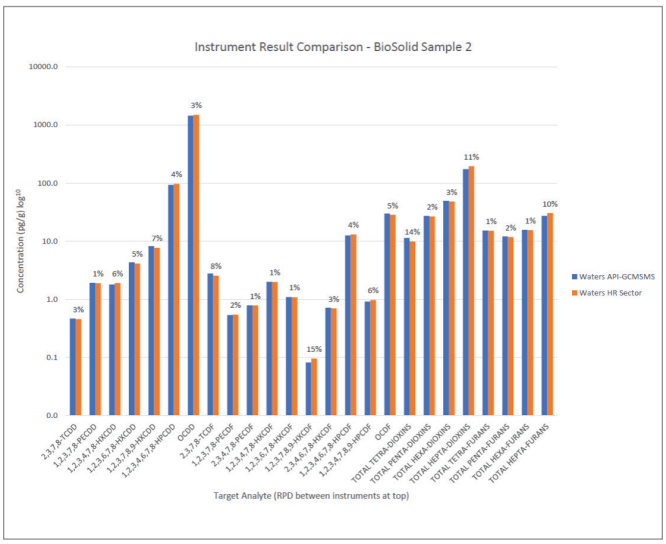


Figure 3. Biosolid sample. Tandem quadrupole (MS/MS) compared with high resolutio n mass spectrometry (HRMS). RPD = Relative percent difference.

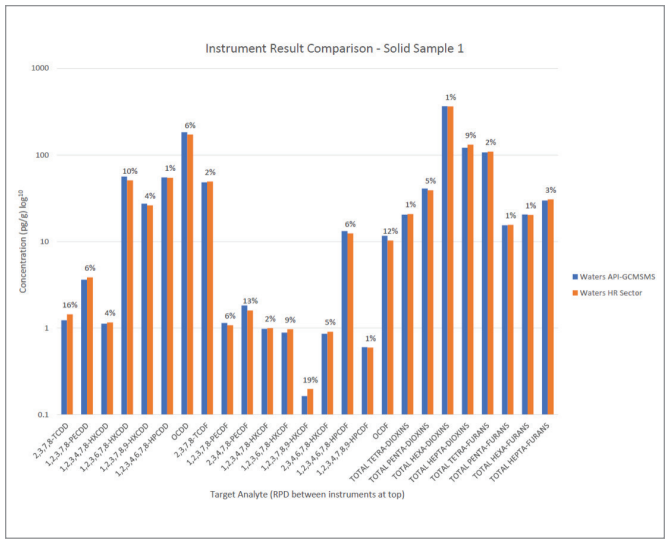


Figure 4. Sediment sample. Tandem quadrupole (MS/MS) compared with high resolution mass spectrometry (HRMS). RPD = Relative percent difference.

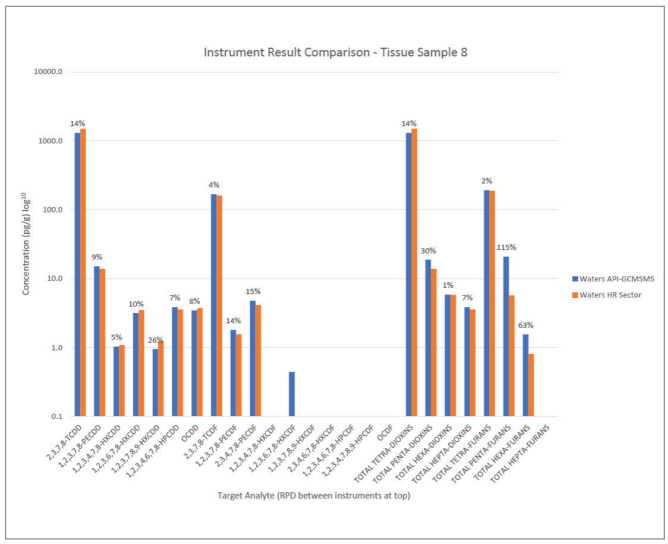


Figure 5. Tissue sample. Tandem quadrupole (MS/MS) compared with high resolution mass spectrometry (HRMS). RPD = Relative percent difference.

The results of this method validation study, being submitted as an Alternate Test Procedure (ATP) to the US EPA, meet the Method 1613B specifications for PCDD and PCDF analysis, and method detection limit (MDL) and initial precision and recovery (IPR) test results showed excellent data quality.

WHAT IS APGC?

- Atmospheric pressure gas chromatography (APGC) is an ionization source that allows most Waters™ Universal source based systems (Xevo™, SYNAPT™, and Vion™) to be coupled with a GC.
- It is a soft ionization technique with high ionization efficiency.
- Allows changeover between LC to GC, enabling complete compound coverage in a variety of applications.
- GC capability is maximized as there is no vacuum restriction, allowing a wider range of GC columns and flow rates to be used.

ADVANTAGES OF APGC FOR DIOXIN ANALYSIS

- A highly sensitive technique for accurate detection and determination of dioxins at regulatory levels.
- Reduced injected volume of samples can minimize matrix effects and the contamination on instrumentation, reducing the need for time-consuming purification steps and increasing uptime, respectively.
- Ability to detect contaminant limits at ultra-trace levels, enabling laboratories to achieve compliance with regulatory limits.
- Reduced cost of testing due to improved sensitivity and selectivity.
- Soft ionization of the atmospheric pressure source reduces fragmentation for many compounds, providing higher sensitivity and selectivity, and simplifying precursor ion selection in MS/MS analyses. Soft ionization is also ideally suited for the analysis of easily degraded compounds.

SUCCESSFUL IMPLEMENTATION OF APGC IN THE FOOD AND FEED INDUSTRY

- **NofaLab – The Netherlands**
  NofaLab is a specialized laboratory based in Schiedem, The Netherlands, offering analysis in the field of food, feed, and environmental safety. Among a vast range of parameters, NofaLab tests for organic contaminants, including dioxins, PCBs, PAHs, and volatile organic compounds (VOC). The ability to analyze contaminants in challenging matrices is a particular benefit for NofaLab, which began using APGC for samples such as edible oil, fatty acids, herbs, and spices. This method also allows the company to expand the number of contaminants it can analyze, with the capacity to examine 500 analytes in one run.

  Many analyses cross the boundary between LC and GC, so the ability of the Xevo TQ-S System to readily switch between the two modalities allows NofaLab to complete screening of a wider range of samples. This is valuable for dealing with compounds with varying physicochemical characteristics, and analysis can be tailored to business demands, maximizing up-time and instrument utilization. Wim Broer, NofaLab science and development manager, explains the benefits his laboratory sees for its customers: *"The pressure for our customers is getting bigger and bigger. Five years ago, this type of analysis could take two or even three weeks. Now, by optimizing the logistics and robust fast methods, we deliver these analytical results within a day."*

- **IQSTAP – Beijing, China**
  Researchers at the Institute of Quality Standard and Testing Technology for Agro Products (IQSTAP)'s Dioxin Testing Laboratory analyze feed agricultural products, and environmental samples affecting these products, using an APGC-Xevo TQ-S System. IQSTAP supports Chinese government agencies and, responding to the tightening regulations on contaminants in feed and food, the laboratory evaluated APGC against the previously used HRGC/HRMS method. Using APGC, the laboratory improved its ability to measure complex matrices, and could confirm trace contaminants at lower levels than previously achievable. APGC was established as a favored alternative as it opens up new possibilities in both quantitative analysis at trace levels and universal screening – both of which require the ability to detect a broad range of contaminants in a variety of matrices. The soft ionization of APGC was a particular benefit for IQSTAP, due to the reduced fragmentation for many compounds when compared with techniques such as EI, and its suitability for the analysis of easily degradable compounds. Reduced fragmentation gave a higher sensitivity and specificity, therefore simplifying precursor ion selection in MS/MS analyses.

  Dr. Xiaomin Li, IQSTAP Assistant Professor, comments on why IQSTAP chose APGC for dioxin analysis, and what is has allowed the laboratory to achieve: *"APGC offers us the advantage of being very easy to operate. APGC compared to HRGC/HRMS is like a photographic card camera vs a Canon high end SLR camera 5D IV. APGC has provided us with new ideas for scientific research. It offers an alternative to traditional GC-MS for dioxin analysis, providing the speed and sensitivity we need."*

CONTINUING DIOXIN ANALYSIS IMPROVEMENT

Since the harmful effects of chlorinated dioxins and furans on human health came to light, the analytical technology used to detect these contaminants at trace levels has undergone steady development, in line with tightening regulatory controls. Despite the limits now in place controlling the emission of dioxins and furans, their production through improper waste burning and natural events is still significant. Additionally, the stable and bioaccumulative nature of these compounds means some of the current exposure can be attributed to historic contamination events. Control measures within the food chain are needed to reduce human exposure to dioxins and furans, including air contamination and agricultural land and water. Reducing the levels of dioxins in feed would have a dramatic impact on contaminant levels in food of animal origin (farmed animals and fish), which is the primary route of human exposure.

Today's detection methods build on the early groundwork made in the 1970s and the subsequent optimizations made over the decades, and dioxin and furan research and detection methods have seen continuous improvement over the past 50 years. As more information becomes available on the structure of congeners and their toxicity and behavior in the environment/food chain, regulatory limits of detection are likely to be lowered and more advanced analytical technology will be required.

The Waters Xevo TQ-XS Mass Spectrometer with APGC.

Methods of preventing and reducing dioxin contamination in the environment, food, and feed are therefore subject to ongoing development and refinement. As concern grows over the need for robust analysis of dioxins and furans in food and environmental samples, more user-friendly technology is essential. The requirement for expert users of magnetic sector instruments has driven the field towards other technologies. Regulatory bodies, as well as responding to technological innovations, react to changing trends and availability in the analytical workforce. The evolution of tandem quadrupole technology as a simpler, more user-friendly alternative to magnetic sector has shifted the pool of operators towards this new technique. Manufacturers and laboratories have responded to address this shift by focusing on fast and robust MS/MS instrumentation to meet analysis requirements.

The new guidance from the US EPA that will allow APGC-MS/MS as a confirmatory tool for checking compliance with ML of PCDD and PCDF represents a key step in method development. Its comparable performance with GC-HRMS, as demonstrated by the method evaluation and validation with SGS AYXS, and its more user-friendly nature places APGC-MS/MS at the forefront of dioxin and furan analysis. Cutting-edge instrumentation, such as the Waters Xevo TQ-XS Mass Spectrometer with APGC, is enabling laboratories in food, feed, and environmental industries to make increasingly sensitive measurements from complex samples, informing contamination incidences, and allowing updated recommendations to be made on regulatory limits. While containment of industrial contaminants and other anthropogenic sources of dioxin and furan emissions are now under better control, the persistence of these compounds in the environment and in living tissue means ongoing developments in analytical technology – such as the move from GC-HRMS to APGC-MS/MS – are required.

For more information on Waters APGC technology, please visit https://www.waters.com/apgc.

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Waters Corporation
34 Maple Street
Milford, MA 01757 U.S.A.
T: 1 508 478 2000
F: 1 508 872 1990
www.waters.com