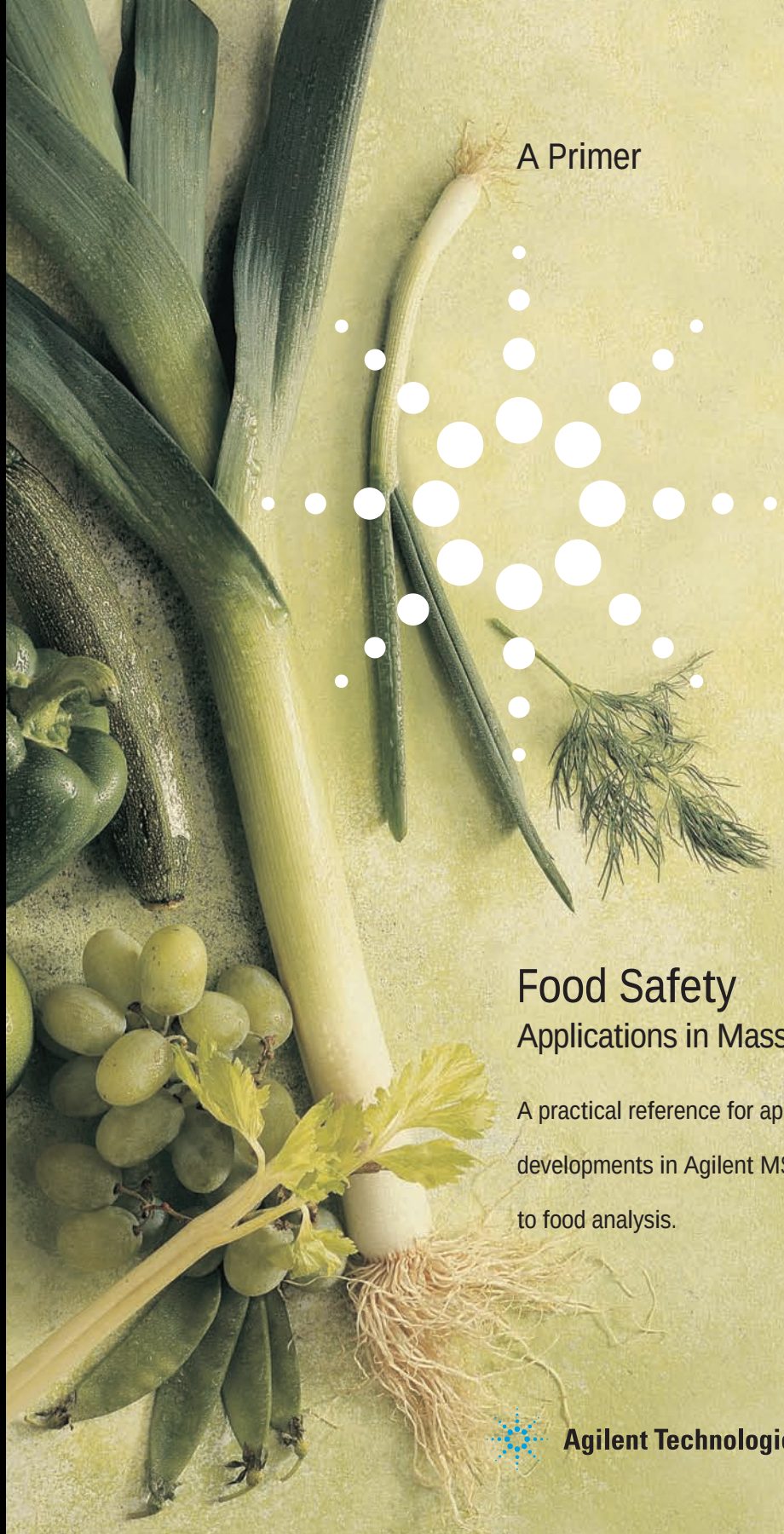
A Primer



Food Safety

Applications in Mass Spectrometry

A practical reference for applying current developments in Agilent MS technologies to food analysis.

Agilent Technologies

Table of Contents

Public safety concerns. International trade regulations. The food industry is under unprecedented pressures to meet ever more stringent food safety standards, regulations, and expectations regarding the chemical residues present in foodstuffs. On the journey from the farm or factory to our plates, many food products will have come into contact with various chemical substances from fertilizers, pesticides, herbicides, growth hormones, and antibiotics, to food additives and migratory compounds from packaging materials.

The Regulatory Framework

Most countries have strict legislation in place governing all aspects of food safety along the entire food production chain. The purpose of setting tough standards is to protect the health and well-being of consumers and to ensure fair trade practices in the global market place. Legislation is often based on international food standards, as set by Codex, Food and Agriculture Organization (FAO), and the World Health Organization (WHO). These organizations aim to establish public health and economic assurances for their member states through promoting the harmonization of methodologies and standards.

Analytical Solutions

Food analysts require analytical methods to detect and identify the nature and concentration of chemicals in all components of foodstuffs from the raw materials to the end product. These sample analyses are challenging due to the complexity of the matrix compounds in food extracts, which often interfere with detection of target compounds and elements.

Traditionally, methods based on high-performance liquid chromatography (HPLC), gas chromatography (GC), graphite furnace atomic absorption spectroscopy (GFAAS), and inductively coupled plasma optical emission spectroscopy (ICP-OES) were commonplace in food-monitoring laboratories. But as regulatory levels are driven down and new analytical challenges arise, analysts require instrumentation that offers low limits of detection with high degrees of accuracy and precision. As a result, more and more laboratories are relying upon detection by mass spectrometry.

Agilent's Mass Spectrometry Capabilities

To address these requirements, Agilent offers a wide range of innovative MS solutions for the analysis of food to complement their chromatography products — take a closer look at the fundamental concepts and instrumental considerations of GC/MS, LC/MS, and ICP-MS in the "Instrumental" part of the Primer.

Each of these mass spectrometry systems is designed to ensure that all food analyses are conducted accurately, reliably, and efficiently, detecting the lowest level of chemicals and elements in complex matrices. Food analysts can draw on Agilent's applications know-how, sophisticated software solutions, high-quality accessories and consumables, and service support to improve sample throughput, solve problems, and deliver reliable results.

Refer to the "Applications" section of this Food Safety Primer for example analyses of some of these substances in foods by an appropriate mass spectrometry technique. Each application features practical information and example performance results.

Find Out More

To keep up to date with developments in this dynamic field, visit the following Web sites:

Agilent Technologies:
www.agilent.com/chem/msfoodsafety

Codex Alimentarius Commission:
www.codexalimentarius.net

Food and Agriculture Organization (FAO):
www.fao.org

World Health Organization (WHO):
www.who.int

Introduction to Mass Spectrometry for Organic and Inorganic Analysis

Mass spectrometry (MS) is an analytical technique which can be applied to the identification and quantification of organic or inorganic constituents in a sample. Although many aspects of the instrumentation used for the analysis of organic molecules is different to that used to measure the elements from the periodic table, the basic principles are the same.

The sample introduction system of a mass spectrometer includes an ionization source that places a small electrical charge on samples converting them to ions. When characterizing organic compounds, it is often important to keep the structure of the molecule intact, so low energy or "soft" ionization processes are used. When measuring elements or metals using mass spectrometry, it is necessary to break down the samples to their fundamental, atomic elements, so a much more powerful ion source is utilized.

Ions produced by the ionization source are separated according to their mass-to-charge ratios using a mass filter and detected with a sensitive detector. The number of ions at each mass-to-charge ratio is collected, and a plot of ion abundance versus mass-to-charge ratio is created. This is called a mass spectrum. Like fingerprints, mass spectra can be used to identify chemical compounds or isotopic composition of a sample.

Mass spectrometry is often combined with a separation technology such as gas chromatography (GC) or liquid chromatography (LC) to form a powerful system for analyzing complex mixtures. The chromatograph separates sample mixtures into their constituent parts. The mass spectrometer then analyzes the sample components to provide data for identification and quantification.

An inductively coupled plasma (ICP) is used as a high-energy source for mass spectrometry for the analysis of trace and ultra-trace elements in a range of solutions. ICP-MS can be combined with a laser ablation (LA) sample introduction device for the direct analysis of solid samples. ICP-MS can also be combined with LC or GC for use as an element-specific detector for many applications.

Agilent's MS portfolio features various kinds of MS instruments built around three main types of mass filter technologies – quadrupole, ion trap, and time-of-flight (TOF) – to meet a variety of needs and applications. Agilent's mass spectrometers are often coupled with the company's industry-leading gas and liquid chromatographs to form powerful GC/MS and LC/MS systems, as well as GC-ICP-MS and LC-ICP-MS systems.

GC/MS Basics

Mass spectrometry (MS) represents the most definitive general detector for gas chromatography (GC) work used in environmental, foods, clinical, pharmacological, and forensic applications. Its wide acceptance is due to its effectiveness in separating, identifying, and quantifying compounds in complex sample-types.

Capabilities of GC/MS

- GC/MS can provide general or specific information
- GC/MS can provide data to identify unknown peaks
- GC/MS can provide data to recognize co-eluting peaks
- GC/MS can provide quantitative information in complex matrices
- A Chemical Ionization (CI) mass spectrum can provide molecular weight information

Requirements for GC/MS

- A key requirement for GC/MS is that the samples have sufficient volatility. The vast majority of the compounds in mass spectral libraries have a molecular weight less than 600. Some higher molecular weight compounds can be derivatized to improve their volatility. In some cases it may be necessary to bypass the GC by introducing the sample with a direct insertion probe.

Principles of GC/MS in Brief

Typically liquid samples are sealed into sample vials and placed in an autosampler. A small volume (usually 1 µL) is injected into the GC. The sample components are vaporized in a stream of helium carrier gas and swept through the column. They are physically separated in the column and emerge at different retention times. Sample peaks from the GC are introduced into a vacuum chamber where the sample molecules are ionized using an appropriate ionization mode – see Figures 1 and 2. The ions produced are accelerated through a mass filter where they are sorted according to their mass-to-charge ratio. The abundance of ions at each mass over a given mass range is measured with a suitable detector. Abundance is plotted against the mass of the fragments to give the mass spectrum. Each compound has a unique spectrum that serves as a fingerprint for that compound. This is the basis for compound identification. The abundance of ions measured in a spectrum is directly proportional to the amount of compound present. This is the basis of quantitative measurements.

Ionization modes

- Electron impact ionization – results in classical spectra for library matching; see Figure 1.
- Positive chemical ionization – produces protonated molecules and adduct ions to confirm molecular weights; see Figure 2.
- Negative chemical ionization – for trace-level detection

Example spectra:

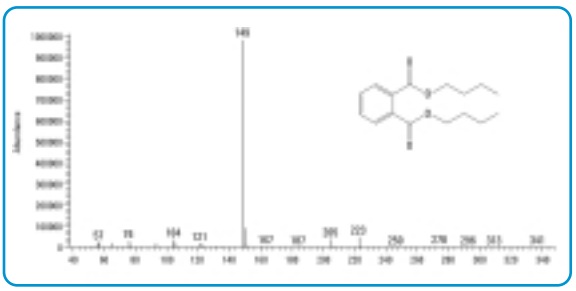


FIGURE 1. MASS SPECTRUM OF DI-N-BUTYL PHTHALATE USING ELECTRON IMPACT IONIZATION (EI). THE MOLECULAR ION IS PRESENT IN VERY LOW ABUNDANCE AT 278 M/Z.

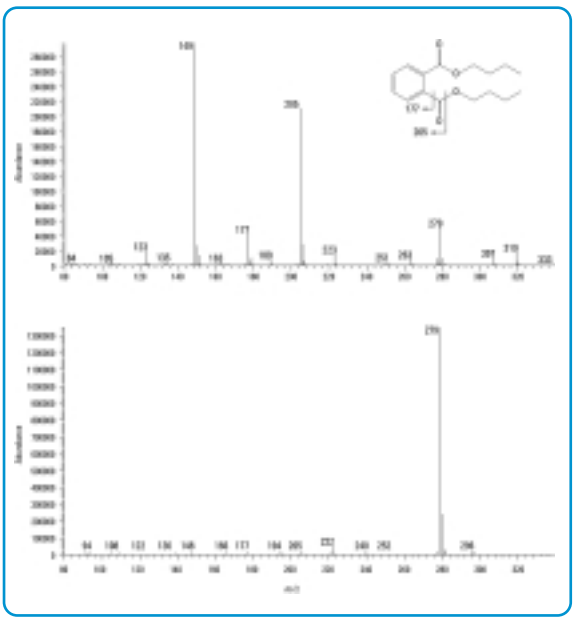


FIGURE 2. MASS SPECTRUM OF DI-N-BUTYL PHTHALATE USING POSITIVE CHEMICAL IONIZATION (PCI) WITH METHANE REAGENT GAS (UPPER) AND AMMONIA (LOWER).

In the spectrum obtained with ammonia (lower), the ion at 279 m/z, indicates $(M+H)^+$ and helps identify the molecular weight. In the spectrum obtained with methane (upper), the ion at 279 m/z, again indicates $(M+H)^+$ and helps identify the molecular weight, but the additional fragments indicate some structural features.

GC/MS instrumentation can be considered under the following five headings:

- Separation
  - Gas chromatography
- Ionization Source
  - Electron ionization (EI)
  - Chemical ionization (CI)
- Mass Analyzer
  - Quadrupole
  - Ion Trap
- Detector
  - Electron multiplier
  - Photomultiplier
- Data System

Separation

Most samples are introduced into a mass spectrometer through a gas chromatograph. Although direct insertion probes are needed for certain specialized applications, GC/MS is the predominant mode of operation. The separation capabilities of the GC far exceed what could be done even with temperature programming of a probe.

Sample Introduction

The first step to producing a mass spectrum is directing molecules into the mass spectrometer through the sample inlet. Gas, liquid, and solid compounds can be introduced into the ion source through specially designed inlets. The most common inlet used in the gas chromatograph is the split/splitless injection port.

In order to use this inlet, the sample must be dissolved in a suitable solvent. Common solvents used in MS are hexane, acetone, dichloromethane and similar volatile, low-boiling liquids. The heated injection port vaporizes the sample and solvent. Therefore, thermally labile compounds are not suited for this inlet. A flow of helium or some other carrier gas directs the components into the analytical column where the components are separated. As with conventional GC detectors, the solvent must be separated from the compounds of interest. Other sample inlets include: programmable temperature vaporizing inlet and cool on-column. With the Agilent cool on-column inlet, it is possible to inject directly into a 250 µm column for maximum sample transfer and minimum degradation. The programmable temperature vaporizing inlet accommodates large-volume injections (LVI) to minimize time-consuming sample concentration steps.

Other devices commonly associated with the GC/MS include the purge and trap and the headspace samplers. Purge and trap samplers work by concentrating volatile components on a packed trap, which is then thermally desorbed onto the analytical column for separation. Headspace samplers, on the other hand, work by injecting a fixed or variable gaseous sample volume onto the analytical column. In both cases the GC oven temperature is set at a low temperature to refocus the analytes, then the oven is ramped to separate them. These sampling devices minimize or eliminate the sample preparation stage.

Column

Modern GC/MS instruments are optimized to work with capillary columns. In older instruments, various devices, such as the jet separator, were used to reduce the column flow to a level suitable for the pumping system. These devices were troublesome to maintain and compromised performance. Fused silica capillary columns were a vast improvement in matching flow rates and providing an inert sample path directly into the mass spectrometer source. The most common column size used in GC/MS is 0.25 mm id, although larger and smaller columns are used. The sensitivity of mass spectrometry is so high that it is highly recommended that the lowest bleed columns be used. Column manufacturers typically have an MS line of some of the most common columns.

Transfer Line

Mass spectrometers are much larger than conventional GC detectors. The connection to the mass spectrometer must be done centimeters away from the GC oven itself. Between the oven wall and the ion source, the column must be maintained at a sufficiently high and uniform temperature that compounds do not condense. Similarly, the temperature cannot be so high that thermally labile compounds degrade. To join the GC oven and the ion source, a heated transfer line is used. The most important characteristics of this transfer line are that it is as short as possible and that it is independently and uniformly heated.

Vacuum System

For proper operation, the interior of the mass spectrometer must be evacuated. The ion source, mass filter, and detector all are under vacuum. The vacuum system makes it possible for ions to move from the ion source to the detector without colliding with other ions and molecules. Typical operating pressures for GC/MS are around 10^{-5} and 10^{-6} torr. This vacuum is achieved by using a high vacuum pump backed by a mechanical rough pump.

Ionization Sources

Sample molecules are introduced into the ion source through the sample inlet. Before the mass spectrometer can analyze a sample, the sample molecule must be ionized. In the ion source, the molecules go through an ionization and fragmentation process. The ions are then directed into the mass filter.

Electron Impact Ionization (EI)

Electron impact ionization (EI) is the most common mode of operation for GC/MS, accounting for over 90% of all work and a high number of commercially available spectral reference libraries. In EI, a molecule emerging from the GC column is ionized by interaction with a stream of relatively high-energy electrons (70 eV). These collisions produce (primarily) positive ions. Upon ionization, the molecules of a given substance fragment in very reproducible patterns. EI is a direct process: energy is transferred collisionally from electrons to the sample molecules. The conditions used result in significant fragmentation of the molecule with the resulting spectrum representing the abundance at various mass/charge ratios; see Figure 3.

This spectral pattern is used to identify the compound. An expert mass spectrometrist may be able to reconstruct the original molecule by looking at the spectrum. Novice users rely on computers to match the unknown spectrum against a database of electron ionization spectra.

Despite excellent instrument sensitivity in full-scan mode for analytes present in the low picogram range of concretations, EI has some limitations. For example, the EI spectrum may not show the molecular ion for some molecules. Also, in some samples there may be insufficient selectivity in EI because of the presence of matrix interferences complicating the spectral information.

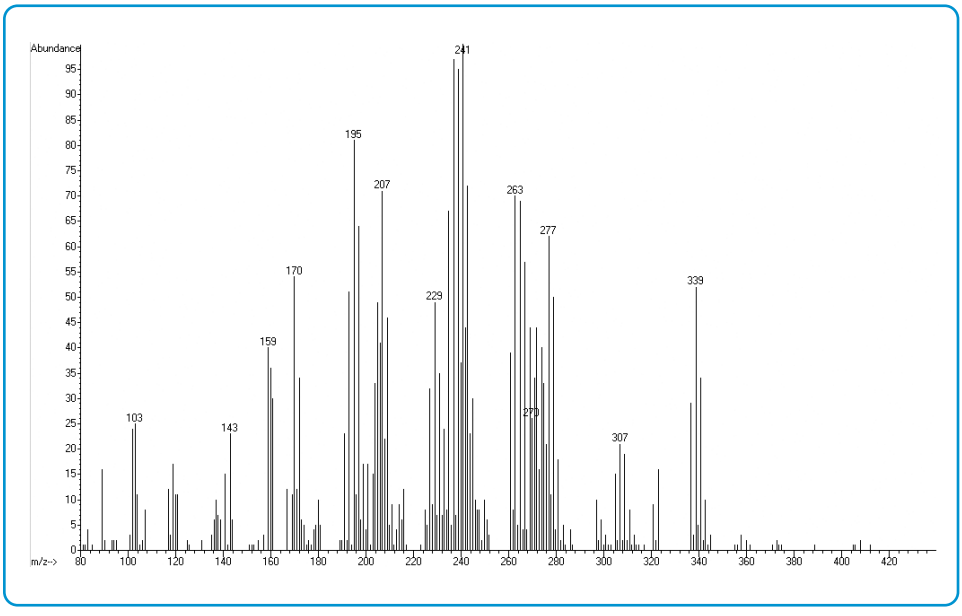


FIGURE 3. MASS SPECTRUM OF THE COMMON PESTICIDE ENDOSULFAN USING EI IONIZATION. NOTICE THE MOLECULAR ION IS OF VERY LOW ABUNDANCE AT 407/408 M/Z AND THERE IS A GREAT DEAL OF FRAGMENTATION.

Chemical Ionization (CI)
Chemical ionization (CI) is another technique that is available to complement EI and extend the use of mass spectrometry. In chemical ionization, sample molecules are introduced into an abundance of reagent gas, typically methane or ammonia. Because there is so much more reagent gas than sample, most of the emitted electrons collide with reagent gas molecules, forming reagent ions. In the case of ammonia, you can get $[M+H]^+$ and $[M+NH_4]^+$ as the products. These reagent gas ions react with each other, in primary and secondary reaction processes that establish an equilibrium. They also react in various ways with sample molecules to form sample ions.

CI ion formation involves much lower energy and is, therefore, much more "gentle" than EI. Because CI results in much less fragmentation, CI spectra usually show high abundance of the molecular ion; see Figure 4. For this reason, CI is often used to determine the molecular weights of sample compounds. In the case of a totally unknown compound, the sample can be run under EI conditions to understand the structure of the molecule and CI conditions to determine its molecular weight. Notice there is an intense molecular anion (M^-) and less fragmentation. The cluster of peaks around the molecular ion indicates there are six chlorine atoms present in the molecule.

In the chemical ionization process, both positive and negative ions are formed. The mass spectrometer can be set up to measure either signal. The selection of the proper ionization method and signal can greatly enhance the signal response. For instance, many compounds that are normally detected using an electron capture detector (ECD) have higher sensitivity in negative chemical ionization than other modes.

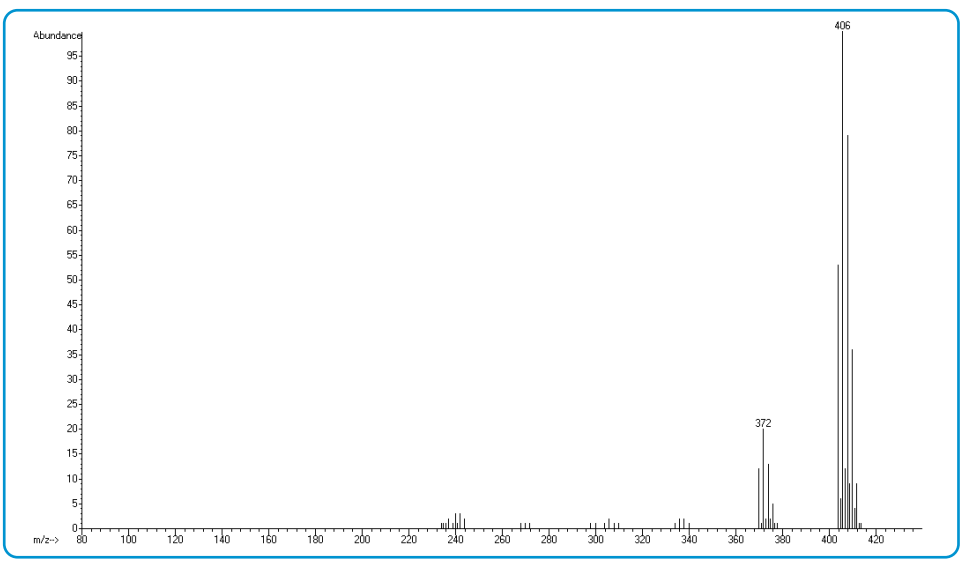


FIGURE 4. MASS SPECTRUM OF ENDOSULFAN USING CHEMICAL IONIZATION WITH METHANE BUFFER GAS.

Mass Analyzers

The ions that are formed either by EI or CI technique must be separated by their mass-to-charge ratio. There are four classes of mass filters (analyzers) that are used to select and filter ions:

- Radio frequency (both quadrupole filter and ion trap)
- Time-of-flight (TOF)
- Fourier Transform: Ion Cyclotron Resonance (ICR or FTMS)
- Magnetic sector

In this section, the principles for quadrupole and ion trap mass filters are discussed. Refer to the LC/MS section for further information on TOF.

Quadrupole (Q)

The quadrupole is the most widely used MS analyzer due to its ease of use, mass range, linear working analytical range for quantitative work, resolution, and quality of mass spectra. Analyses at low picogram levels are routine and data are reproducible, with RSDs of less than 5 percent. A quadrupole mass analyzer consists of four parallel rods arranged in a square (see Figure 5). The analyte ions are directed down the center of the square. Applying precisely controlled DC voltages and a radio frequency to opposing sets of poles generates electrostatic fields that act as a "mass filter." These fields determine which mass-to-charge ratio of ions can pass through the filter at a given DC voltage.

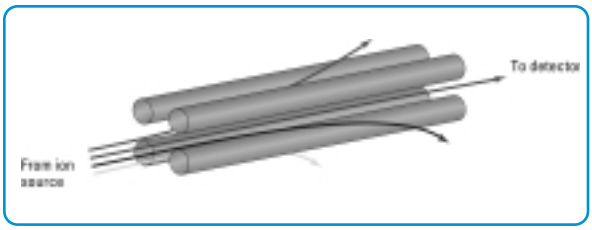


FIGURE 5. QUADRUPOLE MASS ANALYZER

Quadrupole mass analyzers can operate in two modes:

- Scanning (scan) mode
- Selected ion monitoring (SIM) mode

In scan mode, the mass analyzer monitors a range of mass-to-charge ratios. In SIM mode, the mass analyzer monitors only a few ions indicative of particular compounds chosen by the user. SIM mode is significantly more sensitive than scan mode but only provides information about the ions monitored. Scan mode is typically used for qualitative analyses or for quantitation when full spectral information is considered important. Typically SIM mode is used for quantitation of target compounds at the lowest (trace-level) concentrations. Agilent software offers an elegant automated setup of SIM so users can easily develop sensitive GC/MS methods [1].

Ion Trap (IT)
Ion traps have the advantage of being able to perform multiple stages of mass spectrometry (MS/MS or MS^n) without additional mass analyzers. This capability provides useful structural information (identification) and high selectivity and sensitivity in full scan compared to triple quadrupole systems. Triple quadrupole systems are very sensitive in selected reaction monitoring (SRM) mode but not full scan.

An ion trap mass analyzer consists of a circular ring electrode plus two end caps that form a chamber (a 3-dimensional quadrupole). Ions entering the chamber are "trapped" there by electromagnetic fields (see Figure 6). Another field can be applied to selectively eject ions from the trap according to their mass-to-charge ratio (m/z).

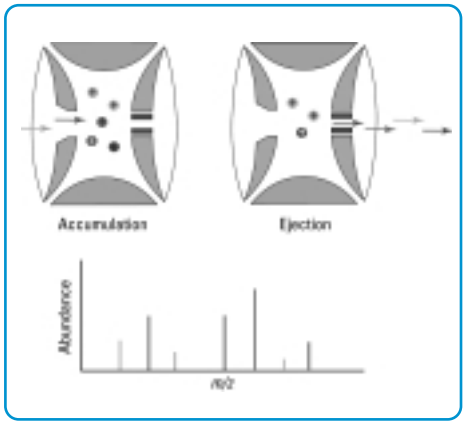


FIGURE 6. ION TRAP MASS ANALYZER

Detector — Electron Multiplier or Photomultiplier

The ions emerging from either a quadrupole or ion trap are detected by either an electron multiplier or a photomultiplier. Only one mass-to-charge ratio ion is detected at a given time. Once inside the detector, the ions generate a signal that is proportional to the total number of ions present. The plot of the mass-to-charge ratio (m/z) of these ions, as a function of abundance, is a mass spectrum.

In an electron multiplier, the incoming ions generate a cascade of electrons which amplify the signal before it is measured. In a photomultiplier system, the ions emerging from the mass filter are converted to photons which are then measured. The electron multiplier is a simpler system while the photomultiplier has the advantage of longer life. Both types of detection systems are used.

Data System

The data system is an integral part of the GC/MS system. Modern instruments cannot be operated apart from the computer that collects the data, displays the results, and generates the reports. Former laborious processes like instrument calibration (tuning) are now automated with software. The computer system also provides diagnostic tools for troubleshooting.

Qualitative Applications

The lines in the mass spectrum represent the mass-to-charge ratio (m/z) of the molecular ion and the fragment ions. An expert mass spectrometrist may be able to interpret this information and identify a molecule by deducing information from its mass spectrum. Using well-documented interpretation methods, mass spectrometrists can identify molecules that are not in a library or database. However, the majority of GC/MS users search the unique spectral pattern with reference library spectra.

In a library search, a computer is used to match an acquired spectrum to a database of spectra by peak matching. This method uses the only two variables available, the mass-to-charge ratios in the spectrum and their relative abundances. Using a computer to do a library search is one way to eliminate a lot of possibilities from a large database of compounds. However, while a spectrum is characteristic of a compound, it may not be unique. Compounds with similar fragmentation patterns (for example, isomers) are difficult to identify based on spectra alone and co-eluting compounds can compromise identification. Retention time locking (RTL) can be used to distinguish between multiple isomers that exhibit very similar mass spectra and therefore require retention time information for confirmation, and spectral deconvolution helps to identify compounds even when they are buried under co-eluting matrix compounds. See RTL and Deconvolution sections on the next two pages for more information.

General mass spectral libraries contain hundreds of thousands of spectra and new data is added constantly. Furthermore, users can create their own libraries of compounds relevant to their work.

Quantitative Applications — Target Compound Analysis

A target ion is an ion characteristic of the target compound, preferably one that distinguishes this compound from any others with similar retention times. The extracted ion chromatogram for this ion will be used for quantitation. Qualifier ions are selected from the mass spectrum of the target compound. The presence of these ions in the correct amounts relative to the target ion gives evidence of correct target compound identification.

Typically, quantitation is based on peak areas (or heights) from chromatographic data generated from the analysis of a calibration standard containing a known concentration of the compound(s) to be quantitated (target compounds). An internal standard (ISTD) is often added to the calibration sample and actual samples. The sample is then analyzed under the same operating conditions. The results are compared to calculate the amount of each target compound in the unknown.

Retention Time Locking (RTL) and RTL Databases

Commercial MS libraries only contain spectral and general information about the compounds. Retention time information is not available. Agilent has provided the capability of using both MS and retention time data through RTL Databases. Retention Time Locking (RTL) is a technique developed by Agilent that allows users to precisely match analyte retention times (RTs) on any Agilent 6890 GC, in any laboratory in the world, so long as the same nominal GC method and capillary column are used [2]. As a result, RTL makes it much easier and faster to analyze target contaminants in complex food matrices.

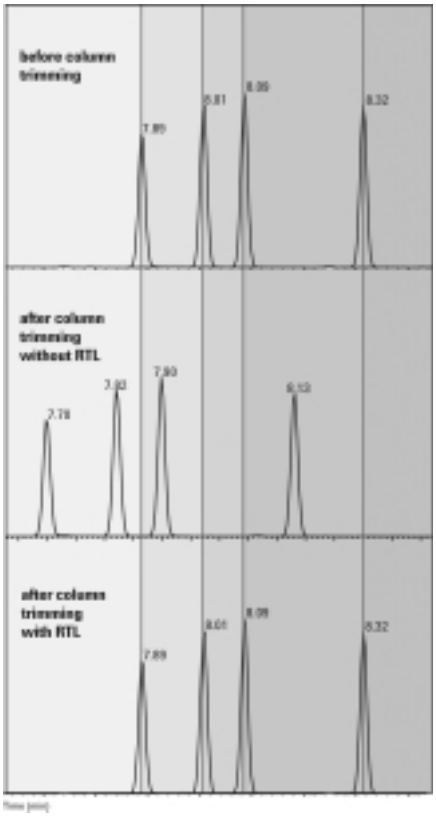


FIGURE 7. THE VARIABILITY IN GC RETENTION TIME, EXPECTED AFTER COLUMN REPLACEMENT OR TRIMMING, IS ELIMINATED WITH RETENTION TIME LOCKING.

RTL calibrates column head pressure and retention time for a target compound. Once done, the method is "locked" and any future deviation in retention time due to column changes can be compensated for by re-adjusting pressure using the calibration — a process known as re-locking. This is demonstrated by removing one meter from a column and performing pressure adjustments (re-locks) to get back to the original target retention time (Figure 7). This is useful for the analyst who has to perform these column cuts frequently in order to remove non-volatile contamination.

Using RTL, Agilent and some users of Agilent instrumentation have developed several retention time locked databases for GC and GC/MS for pesticides, phenols, polychlorinated biphenyls (PCBs), phthalates, and other compound classes [3]. Information contained in the databases may include: locked retention time, compound name, CAS number, molecular formula, molecular weight, and mass spectrum (GC/MS databases only).

For example, the Agilent Pesticide Library contains this information for almost all GC-amenable pesticides, as well as several endocrine disrupters (567 compounds in all) making it possible to screen a GC/MSD data file for all entries in less than a minute. Furthermore, separate Automated Mass spectral Deconvolution and Identification Software (AMDIS) libraries (see next page) have been created from the original Agilent RTL libraries. Users can easily augment these libraries with newer pesticides or other compounds of interest [4].

Deconvolution Reporting Software (DRS) for Complex Matrices

Typical target compound analysis requires finding the target ion and meeting qualifier ion ratios. This is difficult to do in the presence of a high matrix background because ion ratios are affected by the matrix. To be certain of the results, background subtraction and manual integration are often practiced. Consequently, it is a time consuming process to confirm target compounds in a dirty matrix. It can take an experienced analyst more than half an hour to review/confirm one data file.

To aid in the identification process, spectra can be simplified by "cleaning" them mathematically in a process referred to as deconvolution. The mathematical technique "separates" overlapping mass spectra into "cleaned" spectra of the individual components. The National Institute of Standards and Technology (NIST) developed a powerful deconvolution software known as Automatic Mass spectral Deconvolution and Identification System (AMDIS), which is freely available from the NIST website [5].

Agilent has incorporated AMDIS into its Deconvolution Reporting Software (DRS) to create a unique package that combines results from the Agilent GC/MSD ChemStation, AMDIS, and the NIST 2002 Mass Spectral Search Program (NIST02) into a single report. In summary, the Deconvolution Reporting Software performs the following operations in about **one minute**:

- Agilent MSD ChemStation
  - Retention Time Locking (RTL) on 567 target compounds
  - Identification/quantitation of targets based on locked retention time and 4 ions
- AMDIS
  - Identification of 567 targets based on deconvoluted spectra (instead of four ions)
  - Qualify targets based on retention times (using RTL)
- NIST02 Search >147,000 different spectra
  - The component spectra of unknown compounds not in the target library can be searched against the NIST02 main library for identification.
  - Confirm targets using full deconvoluted spectra from AMDIS

DRS contains a 567-pesticide compound library in appropriate formats and is applicable to a range of industries, for example, environmental, food safety, flavors, toxicology, homeland security, PCB analysis, drug testing, forensic, volatiles. Users can tailor the library to their own requirements by adding their own spectra.

References

[1] H. Prest and Dave Peterson, "New Approaches to the Development of GC/MS Selected-Ion-Monitoring Acquisition and Quantitation Methods" Agilent Technologies, publication 5988-4188EN, www.agilent.com/chem.

[2] V. Giarocco, B. Quimby and M. Klee, "Retention Time Locking: Concepts and Applications," Agilent Technologies, publication 5966-2469E, www.agilent.com/chem.

[3] http://www.chem.agilent.com/cag/servsup/usersoft/main.html#RTL.

[4] M. Szelewski and C.K. Meng, "Building and Editing RTL Screener Databases and Libraries," Agilent Technologies, publication 5989-0916EN, www.agilent.com/chem.

[5] National Institute of Standards and Technology, AMDIS Literature and Downloads website: http://www.amdis.net/What_is_AMDIS/AMDIS_Literature_and_Downloads/amdis_literature_and_downloads.html.

LC/MS Basics

Invented more than a century ago, liquid chromatography (LC) is an established analytical method of separating compounds within a sample so they can be identified and quantified. Strengths of the technique are attributable to its sensitivity, quantitative capabilities, and its suitability for separating nonvolatile and thermally fragile molecules typical of 80% of all natural and man-made compounds. With applications in many fields of science and chemical analysis across diverse industries and public services, LC is used to analyze a very wide range of organic compounds, from small molecules, metabolites, peptides, to large, fragile biomolecules such as proteins.

Most applications using mass spectrometry detection will require a separation step so that complex samples are separated into single chemical species to allow:

- Accurate interpretation of mass spectral information — the spectrum must relate to a single chemical species.
- Accurate quantification of an analyte — the mass-specific response must relate to a single chemical species and must be reproducible.
- Interference reduction through effective separation for trace analysis.
- High level of selectivity through use of retention time identification — matching target analyte retention time and related mass spectrum with a target reference standard.

By combining MS with LC, sample components are separated in both time (LC) and mass (MS) to isolate, identify, and quantify any ionizable component in any mixture.

The identification of complex samples presents a problem for LC analysis using traditional detection techniques. Coeluting compounds generally can be identified using UV absorbance detection with diode array technology, but this method may not be specific enough where spectral differences are low. Detection techniques such as fluorescence may offer higher selectivity than UV detection, but if many different compounds are to be analyzed, these techniques also may not yield desired results.

With mass spectrometry (MS), several different analyte classes in a wide variety of sample types can be identified with greater certainty. Although GC/MS is a well-established technique for food analysis, LC/MS is emerging as a useful tool in this area. A GC-based analysis is appropriate only for those food compounds that are volatile and thermally stable. However, many compounds are nonvolatile, extremely polar, or thermally labile. Such compounds often can be separated successfully with LC, and the development of improved interfaces has made LC/MS more popular.

LC/MS instrumentation can be considered under four major stages. The options in each category are not exhaustive but represent the most widely used technologies and demonstrate the number of potential alternatives in LC/MS:

- **Separation**
  Reversed-phase LC
  Normal-phase LC
  Size-exclusion LC
  Ion-exchange LC
  Capillary electrophoresis
- **Ionization Interface**
  Electrospray ionization (ESI)
  Atmospheric pressure chemical ionization (APCI)
  Atmospheric pressure photoionization (APPI)
- **Mass Analyzer**
  Quadrupole
  Ion trap
  Time-of-flight (TOF)
  MS/MS*
- **Detector**
  Electron multiplier
  Microchannel plate

*Multiple-stage MS (also called tandem MS, MS/MS or MS^n) is a powerful way to obtain structural information by fragmenting the ions isolated during the first MS stage, and to achieve better selectivity and sensitivity for quantitative analysis. MS/MS is done:

- Either with an ion trap, by doing multiple experiments within the trap (more cost-effective method)
- or by coupling multiple analyzers

Principles of Mass Spectrometry

Mass spectrometers work by ionizing atoms or molecules, and then sorting and detecting the ions according to their mass-to-charge (m/z) ratios. The key components in this process are the ion source to generate the ions and the mass analyzer to sort the ions. For the mass of an ion to be determined, the ions must pass through the mass analyzer to the detector. At this stage the ions are in the gas phase, and the mass spectrometer is operated under reduced pressure so that the ions can travel to the detector uninhibited. Several different types of ion sources are commonly used for LC/MS. Each is suitable for different classes of compounds. Several different types of mass analyzers are also available. Each has advantages and disadvantages depending on the type of information needed.

Much of the advancement in LC/MS over recent years has been in the development of ion sources and techniques that ionize the analyte molecules and separate the resulting ions from the mobile phase.

The introduction of atmospheric pressure ionization (API) techniques greatly expanded the number of compounds that can be successfully analyzed by LC/MS. As the term suggests, ionization takes place at atmospheric pressure and is considered to be a "soft ionization" method. Following ionization of the analyte molecules, the resultant analyte ions are then mechanically and electrostatically separated from neutral molecules.

Common API techniques are:

- Electrospray ionization (ESI)
- Atmospheric pressure chemical ionization (APCI)
- Atmospheric pressure photoionization (APPI)

Selection of the appropriate LC/MS interface for an application depends on factors such as the polarity, molecular weight, and thermal lability of the analyte (see Figure 1).

In general, ESI is preferred for compounds which are ionic or very polar, thermally labile, or with a molecular weight higher than 100. If you can make a sodium or HCl salt of the compound, then ESI is the preferred ionization source. APCI or APPI are more suited to less polar compounds.

With most LC/MS applications it may be necessary to do positive/negative switching in order to get a response from all components present in the sample.

Electrospray Ionization (ESI)

Suitable for: Molecular weight determination, structure with "up-front" collision induced dissociation (CID), or MS/MS
Applicable to: Large ionic molecules, small singly charged ions
Ionization modes: ESI positive/negative

Electrospray relies in part on chemistry to generate analyte ions in solution before the analyte reaches the mass spectrometer. The LC eluent is sprayed (nebulized) into a chamber at atmospheric pressure in the presence of a strong electrostatic field and heated drying gas. The heat causes further stripping of solvent from the analyte molecules.

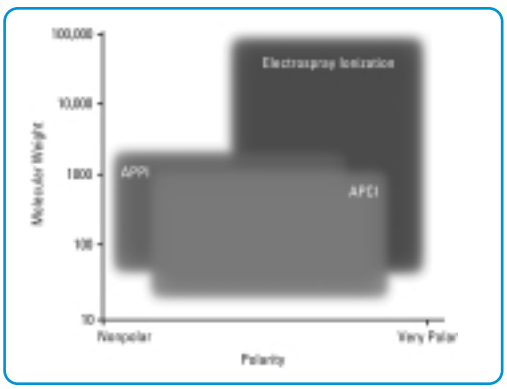


FIGURE 1. APPLICATIONS OF VARIOUS LC/MS IONIZATION TECHNIQUES.

Eventually, the repulsive force between ions with like charges exceeds the cohesive forces, and ions are ejected (desorbed) into the gas phase. The heated drying gas causes solvent clusters in the droplets to evaporate. As the droplets shrink, the charge concentration in the droplets increases, and the above process is repeated. The ions are transported to the mass analyzer through a series of vacuum stages and ion-focusing elements. Some gas-phase reactions, mostly proton transfer and charge exchange, can also occur between the time ions are ejected from the droplets and the time they reach the mass analyzer.

- **Standard electrospray ionization (ESI)** — thanks to multiple charging and low temperatures, electrospray is well suited for analyzing large biological molecules such as proteins, peptides, and oligonucleotides, but it can also be used for smaller molecules.
- **Capillary-flow electrospray** — the capillary-flow electrospray nebulizer is optimized for 1 – 20 µL/min flows, providing increased sensitivity.
- **Nano-flow electrospray** — nanoliter flow rates (50 nL/min to 1 µL/min) and nano columns greatly improve system sensitivity. Electronically controlled flow rates ensure stable ion generation for reliable MS performance.

Atmospheric Pressure Chemical Ionization (APCI)

Suitable for: Molecular weight determination < 2000u, structure with MS/MS or "up-front" collision-induced dissociation (CID)
Applicable to: Ionizable, polar, and nonpolar
Ionization modes: APCI positive/negative

In Atmospheric Pressure Chemical Ionization (APCI), the LC eluent is sprayed through a heated vaporizer (typically 250°C – 400°C) at atmospheric pressure. The heat vaporizes the liquid. The resulting gas-phase solvent molecules are ionized by electrons discharged from a corona needle. The solvent ions then transfer charge to the analyte molecules through chemical reactions (chemical ionization). The analyte ions pass through a glass dielectric capillary and a sampling orifice into the mass analyzer (as with ESI and APPI). APCI is applicable to a wide range of polar and nonpolar molecules. It rarely results in multiple charging, so it is typically used for molecules less than 1,500 u. Due to this, and because it involves high temperatures, APCI is less suited than electrospray for the analysis of large biomolecules that may be thermally unstable. APCI is used with normal-phase chromatography more often than electrospray because the analytes are usually nonpolar.

Atmospheric Pressure Photoionization (APPI)

Suitable for: Molecular weight determination, structure with CID or MS/MS
Applicable to: Compounds less polar than those ionizable by APCI
Ionization modes: APPI positive/negative

Atmospheric pressure photoionization (APPI) for LC/MS is a relatively new technique. As in APCI, a vaporizer converts the LC eluent to the gas phase. A discharge lamp generates photons in a narrow range of ionization energies. The range of energies is carefully chosen to ionize as many analyte molecules as possible while minimizing the ionization of solvent molecules. The resulting ions pass through a glass capillary into the mass analyzer.

APPI is applicable to many of the same compounds that are typically analyzed by APCI. It shows particular promise in applications of compounds not ionized by APCI, such as polyaromatic hydrocarbons.

An APPI source is a useful complement to traditional LC/MS ionization techniques, ionizing samples that ionize poorly or not at all using traditional ESI and APCI techniques.

In all cases, the nature of the analyte(s) and the separation conditions have a strong influence on which ionization technique — electrospray, APCI, or APPI — will generate the best results. The most effective technique is not always easy to predict.

Collision Induced Dissociation (CID)

The atmospheric pressure ionization (API) techniques discussed are all relatively "soft" ionization techniques. The resulting MS spectra consist mainly of "quasi-molecular" (that is $(M+H)^+$ $(M-H)^-$, $(M+NH_4)^+$) ions, unless fragmentation techniques are applied. The resulting molecular weight information is valuable, but complementary structural information is often needed.

To obtain structural information, analyte ions are fragmented by colliding them with neutral gas molecules in a process known as collision induced dissociation (CID) or collision activated dissociation (CAD). Voltages are applied to accelerate the analyte ions to add energy to the collisions and create more fragmentation.

CID can occur in the high-pressure region of the vacuum at the exit of the glass capillary ("up-front" CID), in an rf-only quadrupole designed to have collision gas added to it (a collision cell), or inside an ion trap.

Although any type of mass analyzer could be used for LC/MS, these types are used most often:

- Quadrupole (Q)
- Ion trap (IT)
- Time-of-flight (TOF)

Each has advantages and disadvantages depending on the requirements of a particular analysis.

The mass analyzer separates ions according to their mass-to-charge ratio. The filtration process differs depending on whether the MS is a quadrupole, ion trap, or time-of-flight (TOF).

Quadrupole (Q)
Ionized molecules are guided by a series of lenses into the quadrupole filter. The quadrupole consists of two pairs of rods (or their equivalent) where a direct current (DC) and a radiofrequency (RF) are applied. By controlling the DC and RF, the quadrupole can be set to select the mass-to-charge ratios that can transverse the distance to the detector without colliding into the rods.

A quadrupole mass filter can be operated in a scan mode or select ion monitoring (SIM) mode. In SIM, the mass filter is set to pass one selected m/z. This provides the greatest sensitivity for quantitative applications. It is used when the analyst has prior knowledge of what ions to expect. In scan mode, the mass filter is set to sequentially pass a range of masses. It has lower sensitivity because most of the ions strike the rods during the scan. This mode is used to collect spectra for interpretation or a library search.

Strengths
- Robust operation
- Least expensive analyzer
- Ease of use
- High sensitivity in SIM mode
- Excellent quantitation

Limitations
- Structural information only by "up-front" CID
- Lack of accurate mass information
- Slower scan speed than ion trap and time-of-flight (TOF)

Ion Trap (IT)
An ion trap is another type of mass filter where the ions are stored in a single cavity. The ions are selectively ejected out of the trap and into the detector. While a single linear quadrupole can only perform a single stage MS determination, the ion trap can be used to perform more complex experiments. An ion trap can select an ion and subject it to another cycle of fragmentation. This technique is useful when you need to understand the fragmentation of a particular ion.

Following release from the trap, ions are detected by an electron multiplier. The ability to collect multiple levels of MS data in a single run is one of many advantages of the ion trap. All MS/MS and MS^n data acquired from a run are stored in a single file.

Strengths

- Multiple-stage MS^n
- Fast-scanning capability
- Good resolution
- Full-scan MS/MS sensitivity
- Auto generation of MS/MS with higher sensitivity than triple quadrupole systems (QQQ)
- Well-defined fragmentation pathways from precursor to product ions, allowing more detailed interpretation

Limitations

- No accurate mass information
- Less sensitive than QQQ for low level quantitative studies
- Less fragmentation than QQQ in MS/MS mode because product ions are not further fragmented (however, this makes QQQ spectra more difficult to interpret)

Time-of-Flight (TOF)

Time-of-flight (TOF) mass analyzers have a wide mass range and can be very accurate in their mass measurements with the accuracy and resolution to distinguish empirical formulas (to identify unknown compounds) and separate interfering compounds with the same nominal mass. They are used to provide both molecular weight and detailed structural information for total sample characterization. TOF is particularly suited to the analysis of high mass compounds (500 - $>10^6$ Daltons), e.g., biomolecules.

In a time-of-flight mass analyzer (see Figure 2), a uniform electrostatic force is applied to all ions at the same time, causing them to accelerate down a flight tube. Lighter ions travel faster and arrive at the detector first, so the mass-to-charge ratios of the ions are determined by their arrival times.

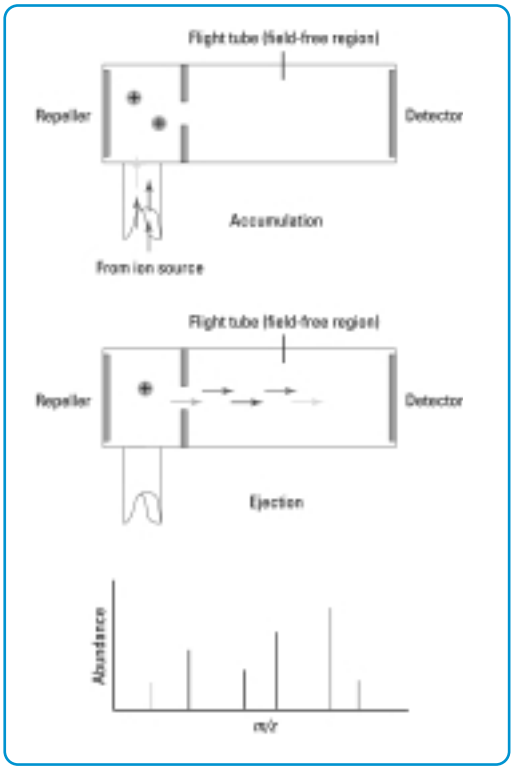


FIGURE 2. TIME-OF-FLIGHT MASS ANALYZER.

Detection Modes
Narrow dynamic range has traditionally been a severe limitation on the usability of TOF MS. New instrumentation, e.g., the Agilent LC/MSD TOF, uses an analog-to-digital conversion that eliminates the dead-time correction needed in many traditional TOF instruments. The result is up to three decades of dynamic range, which eliminates the need to match internal reference mass and sample concentrations. A reference mass can be introduced at a lower concentration for less risk of suppression or interference.

Strengths
- Accurate mass information
- High resolution
- Fast scanning rates
- Good scan sensitivity

Limitations
- No MS/MS capability except with "up-front" CID
- Not as sensitive relative to quadrupole SIM, MS/MS SRM on QQQ, and ion trap

Capillary LC/MS and CE/MS

The mass spectrometry benefits of selectivity and sensitivity are also available to capillary LC and capillary electrophoresis (CE). Capillary LC at microliter to nanoliter flow rates often provides better sensitivity than conventional flow rates for extremely small sample quantities. It is commonly used for protein and peptide analysis but very useful for the analysis of trace quantities of drugs in hair and saliva.

Capillary electrophoresis (CE) is a technique with a high separation efficiency and the added benefit of being able to handle very complex matrices. It has proven useful for such diverse samples as peptides, drugs of abuse, drugs in natural products, flavanoids, and aromatic amines. With specialized nebulizers and method adjustments, electrospray ionization can be used for both capillary LC/MS and CE/MS.

A series of decisions need to be taken in order to identify which LC/MS is the most suitable instrument for the task. It may be useful to consider the following general facts:

- Reversed-phase chromatography is widely used in LC/MS applications.
- Atmospheric pressure ionization techniques (ESI, APCI, and APPI) are widely used in LC/MS.
- Added selectivity* is obtained with MS/MS, e.g., Ion Trap.

Generally LC/MS applications fall into two categories:

- Unknowns – requirement for mass information (molecular weight or fragmentation information). The quantitative aspect is of little or no importance. **Suitable systems include:** QQQ in SCAN mode, Ion Trap, Q-TOF, and TOF with "up-front" CID.
- Suspects and Targets – requirement for very selective and sensitive detection for confirmation and/or quantitation of compounds of known or suspected identity. The molecular weight and the presence of a single ion may be sufficient information. **Suitable systems include:** Q in SIM mode, QQQ in SRM mode, TOF, and Ion Trap.

*Selectivity defines the degree to which other possibilities are eliminated, e.g., the ability to isolate the response of one component in the sample from other components (analytes, interferences, matrix) in the same sample. Higher selectivity is often required for more complex and variable samples.

Specificity defines the degree to which ALL possibilities are eliminated. Compound-specific retention times provide specificity in the separation phase of LC/MS, a prerequisite for identifying target compounds. Specificity in the MS depends on providing a unique response for the target species, e.g., specific fragmentation ion(s) or fragmentation pattern.

ICP-MS Basics

Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is a powerful technique for the measurement of elements in a wide range of sample types. Strengths of the technique include:

- Wide elemental coverage – virtually all elements can be measured by ICP-MS, including alkali and alkaline earth elements, transition and other metals, metalloids, rare earth elements, most of the halogens, and some of the non-metals.
- Performance – high sensitivity and low background signals combine to give very low detection limits (sub-ng/L – parts-per-trillion (ppt) in most cases).
- Fast analysis times – with a high-speed scanning quadrupole analyzer measurement of a full suite of elements takes only about 4 minutes per sample.
- Wide analytical working range – up to 9 orders in a single acquisition.
- Isotopic information.

As the technology behind the technique continues to evolve, ICP-MS is now considered as a viable alternative to ICP-Optical Emission Spectrometry (OES) for fast measurement of higher concentration elements (ug/L to mg/L or ppb to ppm concentrations), while also rivaling or, in many cases, exceeding the detection capability of Graphite Furnace Atomic Absorption Spectrometry (GFAAS) for the determination of trace and ultra-trace elements (ng/L or ppt concentrations).

In summary: ICP-MS can measure a full suite of elements in a single multi-element acquisition, offers a solution to reduce interference effects, accepts almost any sample type, and also provides isotopic information. These capabilities help to explain the widespread acceptance of ICP-MS across all industry types including foods and flavors.

1970's beginnings: Dr. Alan Gray of Applied Research Laboratories in Luton, UK, conducted much of the early research work that led to the commercial development of ICP-MS instrumentation. Gray's early work [1] stimulated research into the use of inductively coupled RF plasmas (ICPs), with some of the key developments taking place in the lab of Velmer Fassel at Iowa State University in collaboration with Dr. Gray in 1978.

1980's first commercial instruments: An important publication by Houk et al. [2] in 1980 demonstrated the possibilities offered by the ICP-MS technique and the first commercial systems followed in the early 1980's.

These systems were composed from parts of two existing technologies – the argon ICP, already in use in ICP-Optical Emission Spectroscopy (OES), and the quadrupole mass spectrometer, then being applied in fields such as gas chromatography mass spectrometry (GC/MS) and residual gas analysis. Although some changes were necessary to allow the ICP to operate in physical contact with the grounded spectrometer interface, the characteristics of these existing technologies were well matched, and the performance of the first systems was impressive.

Present day: ICP-MS technology is still evolving with much of the research and development centered on collision/reaction cell systems to remove plasma (argon) and matrix-based interferences, freeing up the analysis of important elements such as selenium, cadmium, arsenic, and mercury. Elemental speciation analysis using GC and LC coupled to ICP-MS is another important field of development. In many environmental, clinical, and proteomic application areas, it is becoming much more important to be able to determine not just the total amount of a potentially toxic element, but also its chemical form, since this can have a dramatic impact on the element's availability, mobility, and toxicity. In response to this important requirement, Agilent has established integrated solutions to combine gas chromatography (GC), high-performance liquid chromatography (LC), and capillary electrophoresis (CE) with ICP-MS. The speciation "packages" include hardware, software, columns, and proven methodology.

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[2] Houk, R.S., Fassel, V.A., Flesch, G.D., Svec, H.J., Gray, A.L. and Taylor, C. E., 1980, Anal. Chem., 52, 2283–2289

The general principles of ICP-MS are fairly simple and can be broken down into a series of steps as illustrated by the following diagrams:

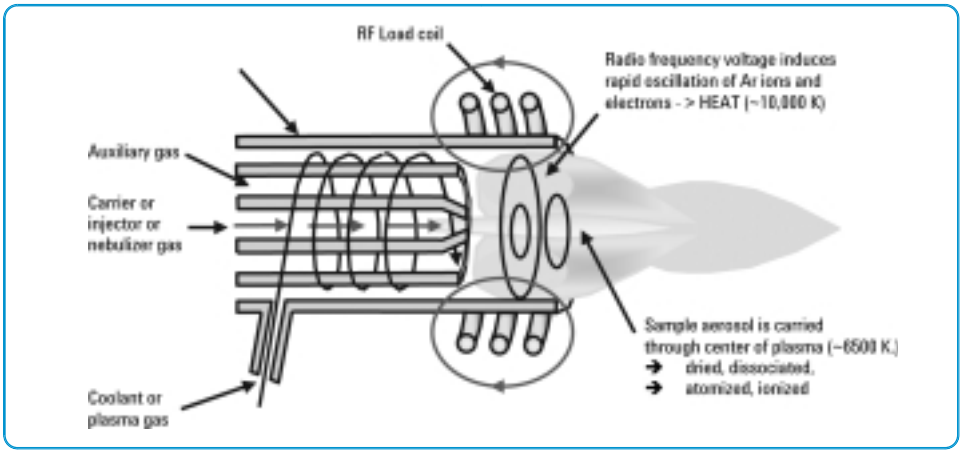


FIGURE 1. DIAGRAM OF ICP TORCH AND PLASMA.

- **Step one:** The sample is introduced into the plasma as an aerosol, usually as a liquid sprayed through a simple nebulizer. In the plasma, the high temperature (6,000–10,000 °K) atomizes and ionizes the sample, creating positively charged atomic ions (see Figure 1).
- **Step two:** The larger aerosol droplets are removed from the gas stream by a spray chamber, and the remaining smaller droplets are swept into the central channel of an argon plasma. The 7500 Series is fitted with a Scott-type spray chamber manufactured from high-purity quartz. Its temperature is precisely maintained with a thermoelectric (Peltier) device to prevent signal drift caused by large changes in room temperature and also to reduce solvent loading on the plasma. This reduced solvent loading leads to a higher plasma temperature, reducing oxide interferences, and aiding in matrix dissociation.
- **Step three:** Sample droplets are dried, decomposed, and dissociated into individual atoms in the plasma. Agilent employs a 27MHz RF generator to provide a high-power (hot) and stable plasma.

  Definition: *A plasma is a gas consisting of ions, electrons, and neutral particles. The electromagnetic interaction between the charged particles creates a very high temperature (6,000–10,000 °K) environment.*
- **Step four:** These atoms are then converted to positively charged ions before being extracted into the vacuum system, via a pair of interface “cones” (see Figure 2).

  Definition: *The cones are essentially metal plates with central orifices through which the ions pass. Small orifices are used, typically 1mm diameter or less, to maintain the high vacuum in the mass spectrometer region and also to restrict the amount of undissociated sample matrix that passes into the high-vacuum region.*

- **Step five:** In the vacuum system, electrostatic lenses keep the ions focused on the central axis of the instrument, as they pass through the vacuum system to the final chamber, where the mass spectrometer and detector are housed. Agilent uses a high-transmission Omega lens arrangement that separates the positively charged ions from the photons and neutral particles, which would otherwise reach the detector and increase random background noise.
- **The final stage:** Analyte ions are separated by the mass spectrometer (MS), which scans rapidly across the mass range and passes each mass of interest sequentially to the electron multiplier (EM) detector. After processing, the output of the detector is a mass spectrum containing the mass and abundance of each ion (Figure 3). Each ion corresponds to an individual element or isotope in the original sample, and the abundance is directly proportional to the original concentration.

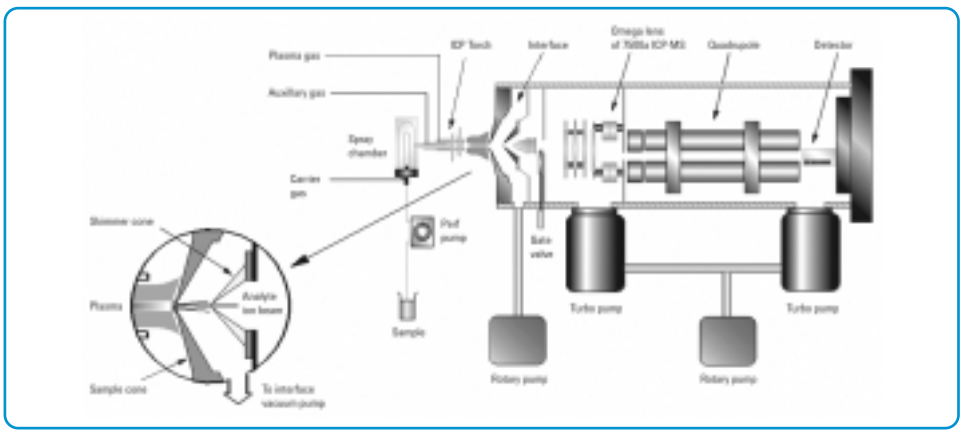


FIGURE 2. DIAGRAM OF AGILENT 7500 SERIES ICP-MS INSTRUMENT. DEPENDING ON THE MODEL, THE OMEGA LENS OR OCTOPOLE REACTION SYSTEM (ORS) MAY BE PRESENT.

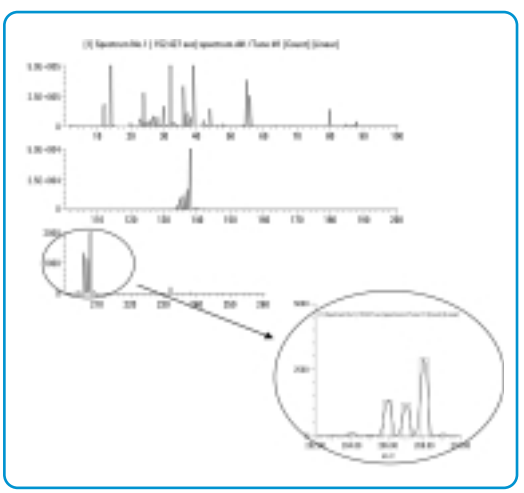


FIGURE 3. FULL SCAN MASS SPECTRUM OF SPIKED CINNAMON EXTRACT SHOWING RELATIVE ABUNDANCES OF ELEMENTAL CONSTITUENTS. ENLARGEMENT SHOWS ISOTOPE RATIOS OF 10-PPB LEAD.

As a result, the ICP-MS spectrum is a simple, accurate representation of the elemental composition of the sample. ICP-MS offers a number of advantages over other elemental analysis techniques. The most important are its extreme sensitivity, selectivity, and simultaneous multi-element capability. No other technique can deliver part-per-trillion (ppt) or sub-ppt detection limits (DLs) for almost the entire periodic table in a single scan taking just a few minutes. The only elements that are not directly measurable by ICP-MS are hydrogen, helium, neon, argon, and fluorine.

Although ICP-MS is a powerful multi-element technique with many celebrated attributes, including high sensitivity and selectivity, some elements in certain matrices are subject to interference by matrix-based polyatomic interferants. Collision and Reaction Cell (CRC) processes can extend the range of applications for ICP-MS in routine and research laboratories by removing these problematic interferences.

Origins of Cell Technology

The collision cell technology used in the Agilent ICP-MS systems is derived from organic mass spectrometry, where organic molecules are either fragmented to give information about structure, or modified by reaction to allow information to be extracted on ion molecule reaction processes.

While the hardware and configuration of the cells used in ICP-MS have many similarities to the organic MS version, the function is quite different. In ICP-MS, the primary function of the cell is to modify the composition of the ion beam, in such a way that interfering polyatomic species are moved or neutralized, or the analyte itself is moved to an alternative, interference-free mass.

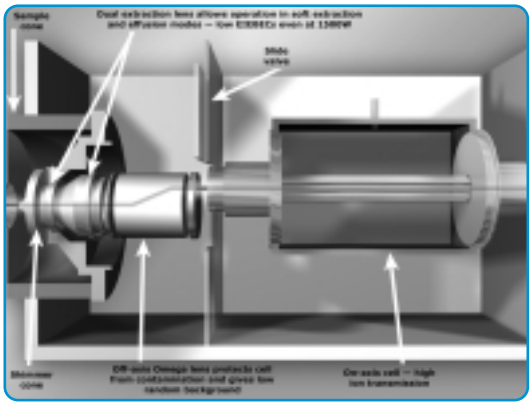


FIGURE 4. SCHEMATIC OF AGILENT 7500CE AND 7500CS ICP-MS SHOWING THE OCTOPOLE REACTION SYSTEM (ORS) CELL.

Application of Collision/Reaction Cell Technology to ICP-MS

Agilent uses an Octopole Reaction System (ORS) in the 7500ce and 7500cs models of ICP-MS. The ORS is an octopole ion guide with excellent transmission properties. It is mounted on-axis to the quadrupole for high ion transmission, as shown in Figure 4.

Agilent's cell-based ICP-MS instruments can be operated in any mode, or a combination of three different modes, all under computer control:

- **Normal mode** — the instrument performs like a standard ICP-MS. High sensitivity is achieved for all of the elements with the exception of those that are susceptible to isobaric interference. This mode would typically be used for Be, Co, Hg, Pb, etc.
- **Reaction (hydrogen) mode** — used for elements that are subject to interferences originating in the plasma (Ar on ^{40}Ca, ArO on ^{56}Fe, ArAr on ^{78}Se). In this mode, interferences are "reacted" away by protonation or charge transfer before entering the mass filter region. An example of this would be as follows:

$$Ar^+ + H_2 \rightarrow Ar + H_2^+$$

In this example the ionized argon is neutralized by H_2 which then allows for the measurement of Ca at mass 40.

- **Collision (helium) mode** — used in the case of elements that are subject to interferences originating from the sample matrix (ClO on ^{51}V, ArC on ^{52}Cr, NaAr on ^{63}Cu, ArCl on ^{75}As). By means of either collisional dissociation or kinetic energy discrimination (KED), the interference can be removed. In the collision mode the interfering complex is broken apart by repeated collisions with the He gas. Also, since these polyatomic interferences have larger cross-sectional areas than the elemental ions of interest, repeated collisions with helium reduce the kinetic energy enough so that they don't reach the mass filters.

The flow for hydrogen or helium into the cell is commonly set to approximately 4–6 mL/min. The hydrogen or helium gas is introduced into a small region between the interface (sample/skimmer cones) and the mass filter (quadrupole). This region contains the octopole ion guide which serves two purposes. As the name implies, it guides ions generated in the plasma towards the mass filter where they can then be measured. It is also a small, contained region within which reactions or collisions can take place to effect the processes described above.

In either the hydrogen or helium modes, an overall reduction of counts is observed for both analytes and interferences. The gain in sensitivity is accomplished by the fact that the reduction of interference counts occurs at a much greater rate as a function of gas flow (H_2 or He) than does the reduction of analyte counts. This attenuation of signals can be used to extend the linear range of elements that are normally present at much higher levels in, for example, environmental samples. Therefore, the helium and hydrogen modes can be used for elements such as Na in order to allow calibrations up to 1000ppm.

Application of ORS-ICP-MS for Routine Analyses

Collision/reaction cell ICP-MS can be a powerful tool for routine analysis of complex samples. Pressurizing the ORS with an inert gas such as helium offers the benefits of interference removal for both semiquantitative screening mode and full quantification mode under a single set of conditions for all analyte elements. In addition, analytes that suffer from compound interferences (several matrix-based polyatomics at the same mass) can be quantified accurately, as all polyatomic ions are reduced under the same conditions, without analyte loss or forming new cluster ions.

Practicality is extended to operation in reaction (hydrogen) and normal mode. Once the ICP-MS has been tuned, the operating conditions remain the same despite the acquisition mode being used. Switching the ORS gas mode is controlled from the software, and all results are collated into a final data report. ORS-ICP-MS is also compatible with chromatographic separations, allowing measurement of ultra-trace level species of Cr, As, Se, etc., after separation using CE, LC, or GC.

Interference Removal by Reaction — Different Approaches

An alternative method of interference removal is by reaction only. Reaction processes occur in any cell when a reactive gas, such as H_2, CH_4 NH_3, etc., is used to pressurize the cell. Very reactive and heavy gases, such as NH_3 and CH_4, can remove polyatomic interferences with a high degree of efficiency and are principally of use for determinations in high-purity samples, such as semiconductor process chemicals. This is because these reactive gases are relatively nonspecific and will react efficiently with many polyatomic ions, analyte ions, and matrix ions, based on the thermodynamics of the various reaction processes which might occur between any given ion/molecule pair [1]. As a result, the use of very reactive (and nonspecific) cell gases can potentially lead to the formation of a large number of new polyatomic ions when complex samples are measured.

To overcome this limitation and permit the use of these reactive gases, one commercial cell configuration, known as a Dynamic Reaction Cell (DRC), uses a quadrupole as the cell ion guide, which allows the stability regions within the cell to be controlled in such a way as to reject ions a set mass below and above the target analyte mass. This is known as a "band-pass" filter, and its function is to stop the newly formed cluster ions from appearing in the mass spectrum and causing new interference overlaps.

It should be noted that the use of a band-pass filter to reject newly formed and potentially interfering polyatomic or cluster ions does not stop the formation of such ions. This means that the reported high reaction rate of analytes (such as As^+ and Ni^+) with highly reactive gases (such as NH_3) does, in practice, lead to analyte loss.

References

[1] Hattendorf, B. and Gunther, D., 2000, J. Anal. Atom. Spectrom., 15, 1125–1131

Techniques

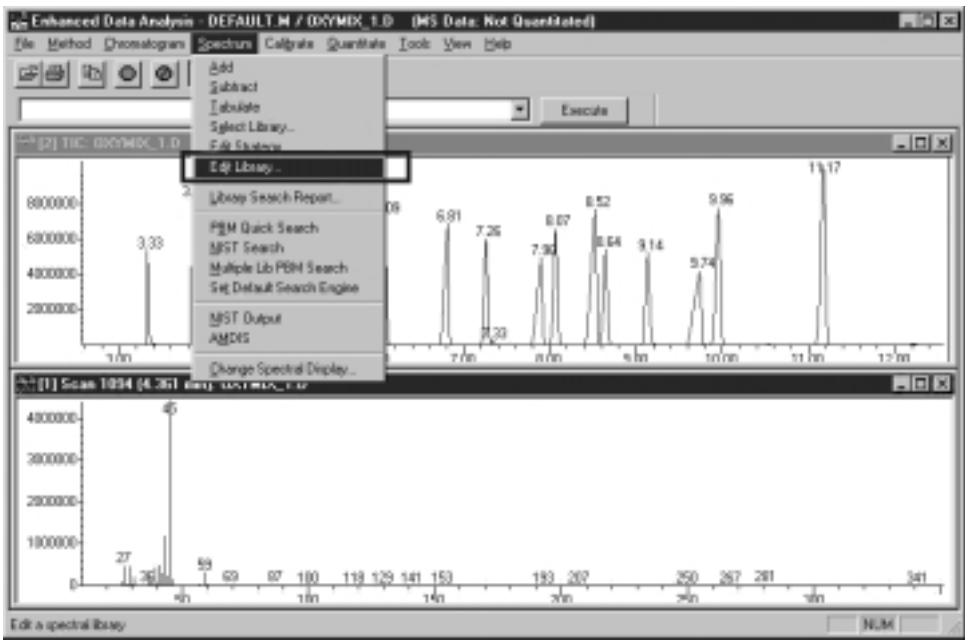
Agilent's portfolio of food analysis solutions encompasses state-of-the-art instrumentation based primarily on mass spectrometry techniques plus sophisticated software packages. Each system is designed to deliver the highest level of performance, while retaining ease of use, flexibility, and reliability demanded by food analysts all over the world. Innovations include the powerful Retention Time Locking software tool and improved acquisition methods for GC/MS. System innovations include the LC/MSD TOF for identification of uncharacterized compounds and ICP-MS with Octopole Reaction System (ORS) technology for trace level quantification of elements in the most challenging sample matrices.

Building and Editing RTL Screener/Quant Databases and Libraries

The powerful software techniques of Retention Time Locking (RTL) [1], Target Compound Screening [2], and Deconvolution Reporting [3] all use retention times (RTs) for an additional level of compound confirmation. It is important for maximum productivity and quality that RTs are constant/reproducible and embedded in mass spectral libraries [4]. However, not all compounds are in a commercially available mass spectral library, and most mass spectral libraries do not have RTs.

Using Agilent GC/MS ChemStation and Microsoft Excel, analysts can follow step-by-step instructions to build (add compounds) and edit RTL Screener databases, RTL Quant databases, and Mass Spectral Libraries.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0916EN.



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[4] K. Weiner and H. Prest, "Retention Time Locking: Creating Custom Retention Time Locked Screener Libraries," Agilent Technologies, publication 5968-8657E www.agilent.com/chem

Comprehensive Pesticide Screening by GC/MSD using Deconvolution Reporting Software

Typical target compound analysis requires finding target ions and meeting qualifier ion ratios. It is always very difficult to identify target compounds from a high matrix background because the matrix affects the ion ratios of the target compounds. Background subtraction and manual integration are often required to be certain of the results. This is a time-consuming process; it can take an experienced analyst an hour to review/confirm one data file.

Two powerful GC/MS techniques — Retention Time Locking (RTL) and peak deconvolution — have been combined to create a quantitation and screening tool that can identify 567 pesticides and endocrine disrupters from a single run in a minute or two.

Increase Confidence with Combined Report

The Deconvolution Reporting Software (DRS) for target compound analysis combines the results from Agilent ChemStation, AMDIS, and the NIST 2002 Mass Spectral Search Program (NIST02, >143,000 compounds) into one easy-to-read report, shown in Figure 2.

Pesticides in an Herbal Mix

Figure 1 shows a total ion chromatogram (TIC) from the extract of an herbal mix. This sample was chosen because herbs are among the most difficult vegetable products to analyze. Their extracts contain a large number of natural products that interfere with pesticide analysis.

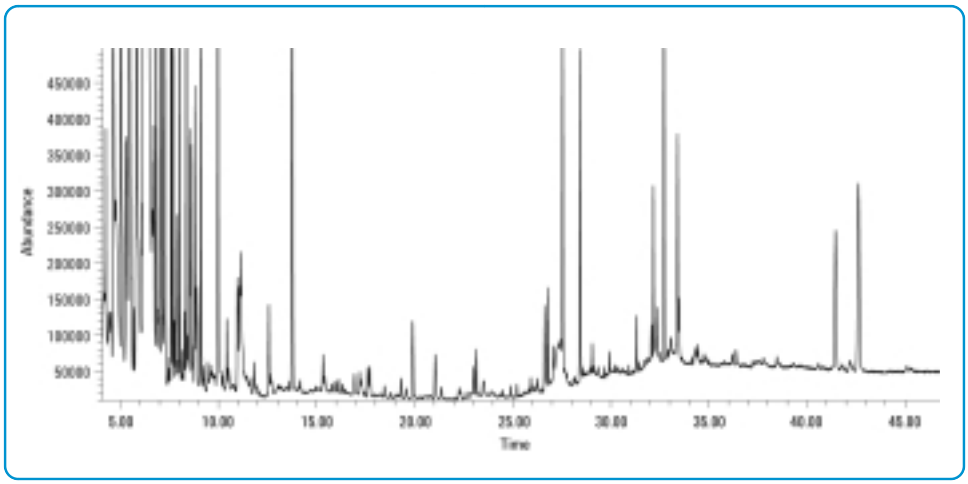


FIGURE 1. TIC OF AN HERBAL MIX.

Comprehensive Pesticide Screening by GC/MSD using Deconvolution Reporting Software (continued)

The DRS report in Figure 2 lists the RT, CAS number, and compound name for each hit. Column 5 in the report shows the match factor obtained through AMDIS deconvolution and RTL Pesticide Library searching using the deconvoluted full spectra. In this case, several more targets were identified by AMDIS than were found by the ChemStation software, which is typical for complex samples. When locked RTs are available, it is a significant advantage to set an RT requirement in the AMDIS software. In this case, hits that did not fall within ±10 seconds of the database RT were eliminated. Column 6 shows the RT difference (in seconds) between the compound's library RT and its actual value in the chromatogram.

The last two columns in the DRS report show the results from searching all of the AMDIS hits against the NIST 147,000-compound mass spectral library. When the NIST library search finds a compound in the top 100 matches (a user-settable value) that agrees with the AMDIS results, its match factor is listed in column seven. The hit number is shown in the last column, with "1" being the best match (highest match factor) in the NIST database.

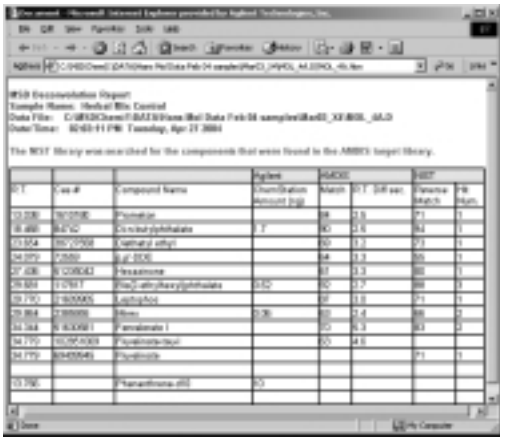


FIGURE 2. MSD DECONVOLUTION REPORT GENERATED FOR THE HERBAL MIX EXTRACT SHOWN IN FIGURE 1.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-1157EN.

New Approaches to the Development of GC/MS Selected Ion Monitoring Acquisition and Quantitation Methods

Operating a GC/MS in selected ion monitoring (SIM) mode leads to a sensitivity increase for target analytes through the selective detection of ions most indicative of the compounds of interest. GC/MS-SIM methods are useful and widely applied, although they can be complicated to develop and maintain, especially when the compound list is long. The AutoSIM feature of the Agilent Mass Selective Detector Productivity ChemStation software and retention time locking (RTL) reduces the difficulty in managing SIM acquisition and quantitation databases. RTL makes retention times permanent despite column maintenance or even replacement.

Example

Figure 1 shows a GC/MS total ion chromatogram for 83 compounds that are part of the EPA 8270 method. Notice the separation is very poor in the 6-to-13-minute region. Applying the defaults of the SIM setup produces 13 SIM groups and a warning that there are too many compounds for use of all the quantitation ions in the 3rd and 4th groups. Reviewing the SIM Ion Report shows there is not enough time between peaks to start a group. This means looking for the largest gap between the end of one peak and the beginning of another will guide setting a shorter "Minimum Time Between a Peak and a Group Start" parameter. There are two approaches: review the gaps and find the largest gap and divide by two to find a new time parameter or the easier approach of iteratively shortening the minimum time by 0.01 increments. Shortening the "Minimum Time Between Peak and Group Start" parameter increases the number of groups and eventually generates a method which allows for all the ions. Notice this has 19 SIM groups as shown in Figure 1.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-4188EN.

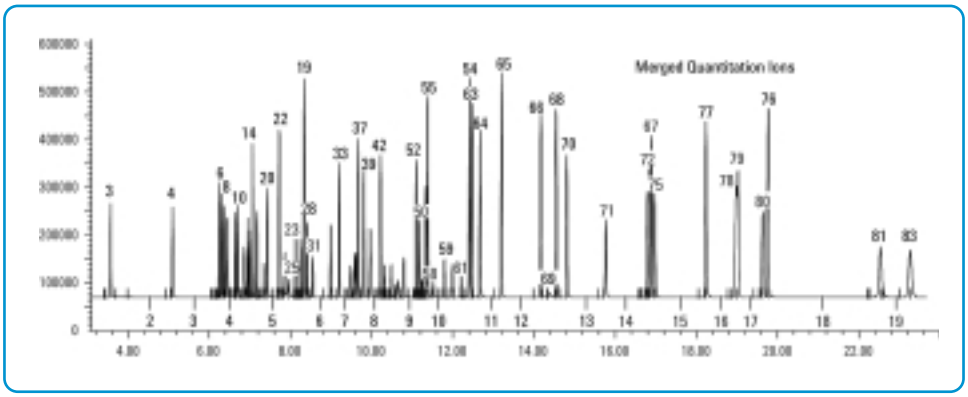


FIGURE 1. MERGED QUANTITATION ION CHROMATOGRAM OF THE HIGHEST STANDARD IN A SIM METHOD GENERATED BY THE SIM SETUP SETTINGS WITH A SHORTER TIME FOR THE "MINIMUM TIME BETWEEN PEAK AND GROUP START" PARAMETER. THERE ARE 19 SIM GROUPS TO ACCOMMODATE ALL THE COMPOUNDS.

Analyzing Phenyl Ureas and Carbamate Pesticides Using ESI-, APPI-, and APCI-LC/MSD

Carbamates (a class of highly effective insecticides) and phenyl ureas (a class of herbicides) are potential endocrine disrupters found in ground- and surface-water samples. Due to the thermally labile nature of these compounds, liquid chromatography is the method of choice for the separation of these compounds and mass spectrometry (MS) the preferred detector choice providing better sensitivity and specificity than typical diode array detectors (DAD).

Both classes of compounds were analyzed by LC/MS using electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), and atmospheric pressure photo ionization (APPI) sources. APPI and APCI have lower background signals and fewer background peaks than ESI. Figure 1 compares the signal to noise (S/N) of some of the target compounds analyzed by the three sources. The figure shows that carbamates, in general, give better S/N from ESI than from APCI or APPI. However, it is just the opposite for phenyl ureas; for example, the S/N is better from APCI or APPI than from ESI. It is also worth noting that APPI shows consistently higher S/N than APCI for this study. A small amount of post-column acetone was needed in the APPI source as a dopant. The dopant is photoionizable and is used to transfer charge to the analyte.

A calibration curve was generated based on the Methomyl $[M+H]^+$ (m/z 163) using ESI in Selected Ion Monitoring (SIM) mode. The curve is linear over the concentration range of 20–2,000 pg on-column with the linear correlation coefficient of 0.9996.

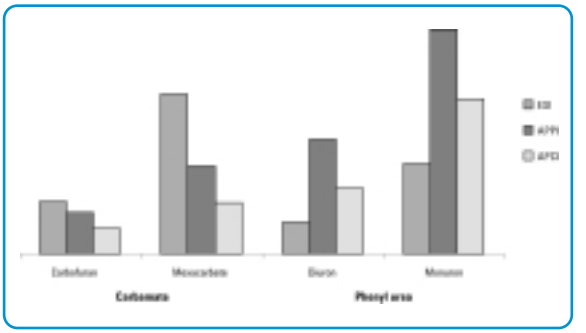


FIGURE 1. THE SIGNAL : NOISE (S/N) OF FOUR ANALYTES FROM THE THREE IONIZATION MODES.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-6635EN.

Identification of Unknowns using the Agilent LC/MSD TOF

Atmospheric pressure ionization time-of-flight (API-TOF) MS can be used for identifying true unknowns. Identification is based on the generation of an accurate mass for the protonated molecular ion that is sufficient to determine the correct empirical formula. This high-precision technique does not depend on fragmentation, although fragmentation data derived using the ion trap or by up-front collision-induced dissociation in the single quad is complementary and helpful.

Processed Waste Water Sample
A 20-µL portion of a process in-feed water sample for drug analysis was injected into the ESI-TOF-MS, under optimized conditions. Appropriate extracted ion chromatograms (EICs) were generated and are shown in Figure 1. EICs compatible with expected retention time (RT) and nominal mass are shown.

Environmental and Food Safety
Confirmation of suspected "HITS" by accurate mass measurement is an accepted and respected "high-end" technique. Identification of true unknowns is greatly aided by accurate mass TOF, complementing trap fragmentation data. A trap for target compound screening followed by TOF confirmation is a powerful combination.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0626EN.

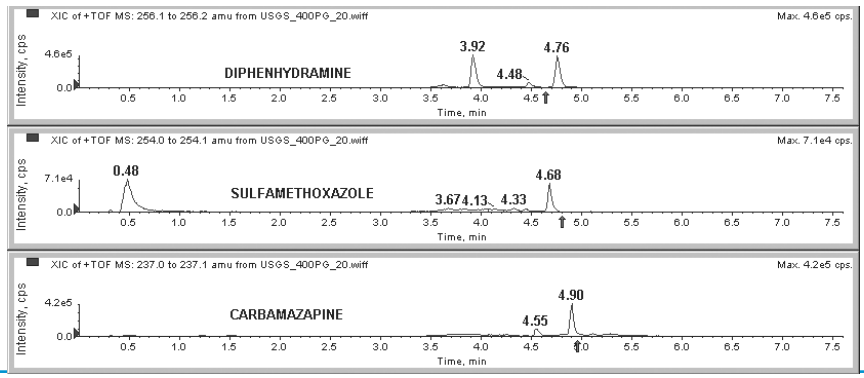


FIGURE 1. STACKED EICs FOR WATER SAMPLE 119, FOR DIPHENHYDRAMINE, SULFAMETHOXAZOLE, AND CARBAMAZAPINE. THERE ARE THREE POSSIBLE HITS SINCE MASSES AND RTs MATCH EXPECTATIONS.

Analysis of High Matrix Environmental Samples with the Agilent 7500ce ICP-MS with Enhanced ORS Technology

It is generally perceived that ICP-MS cannot handle the analysis of samples containing high amounts of total dissolved solids as well as graphite furnace atomic absorption (GFAA) and ICP optical emission spectroscopy (ICP-OES). The principal obstacles to the full adoption of ICP-MS for this application have been overcoming matrix interferences, increasing linear dynamic range and improving instrument stability. Although collision/reaction cells (CRCs) are available to remove matrix interferences, many ICP-MS instruments have a limited ability to handle the effects of high matrix samples on the plasma, interface, and mass spectrometer of the ICP-MS. The Agilent 7500ce Octopole Reaction System (ORS) was designed specifically to address these challenges.

Analysis of Interference Check Samples
US EPA interference check samples (ICS-A and ICS-AB) were used to simulate a challenging high matrix reference material. ICS-A contains high concentrations of elements known to cause interferences in ICP-MS. It is intended to test the ability of the ICP-MS system to handle high matrix level samples and minimize matrix interferences. ICS-A also contains sufficient total dissolved solids to test the robustness of the ICP-MS interface and ion optics to salt buildup. ICS-AB is a spiked ICS-A sample intended to test the ability of the system to accurately detect low-level analyte elements in this challenging matrix.

A total of eight analyses each of ICS-A and ICS-AB were included in a 15.5 hour sequence of high matrix samples. Also included were 13 calibration check samples (CCVs) to monitor the long-term performance of the instrument (Figure 1). All elements demonstrated excellent recovery, and all CCVs were within the EPA limits of +/- 10 percent for the entire run. CCV precision for the 15.5 hour run was in the 1–2% range.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0915EN.

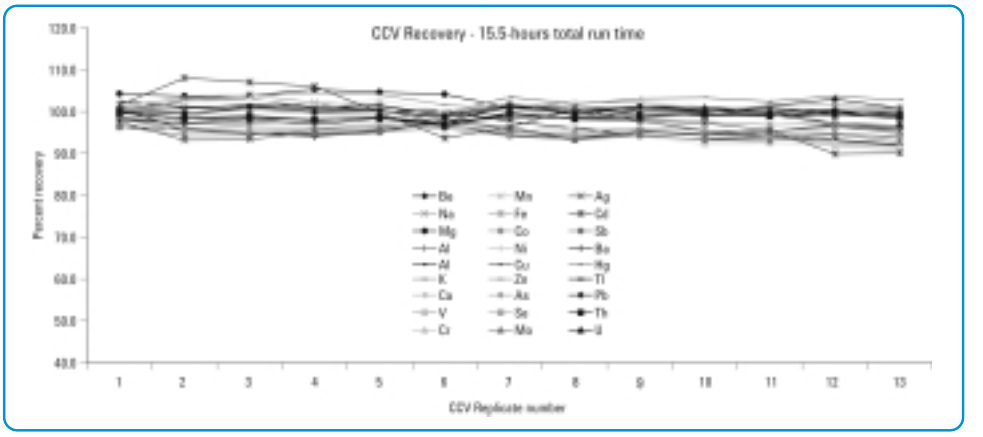


FIGURE 1. RESULTS OF 13 SEPARATE ANALYSES OF THE CCV SAMPLE OVER THE 15.5 HOUR SAMPLE SEQUENCE. ALL ANALYTE ELEMENTS ARE REPORTED. ACCEPTABLE CONTROL LIMITS ACCORDING TO US EPA METHOD 6020 ARE +/- 10%.

Foods

Agilent's instruments, systems, and supplies are used throughout the food production chain, including incoming inspection, new product development, quality control and assurance, and packaging. Innovative instrumental and software data-handling developments, such as the LC/MSD Trap XCT and TOF, ICP-MS with Octopole Reaction System technology, and Retention Time Locking, help analysts solve problems more reliably, more efficiently, and with higher quality results than ever before.

GC/MS Approaches to the Analysis of Acrylamide in Foods

The discovery of acrylamide (2-propenamide) in fried and baked foods at levels many times that allowed in water suggested a much higher exposure than previously estimated. Acrylamide, a known neurotoxin, is considered a probable human carcinogen. The World Health Organization considers 0.5 µg/L the maximum level for acrylamide in water. However, foods such as french fries, baked potato chips, crisp breads, and other common cooked foods were found to contain acrylamide between 100 and 1000 µg/kg. Recent work has suggested that acrylamide forms via the Maillard reaction, which occurs when amino acids and sugars (for example, asparagine and sucrose) are heated together. The concern over these relatively high concentrations has led to studies of the occurrence of acrylamide in a wide variety of foods.

Rapid Screening via GC/MS-SIM with Positive Chemical Ionization

A wide variety of instrumental approaches has been applied to acrylamide analysis, including a simple GC/MS-SIM approach with positive chemical ionization (PCI) which provides good selectivity and picogram-sensitivity for acrylamide.

Figure 1 shows the extracted ion chromatograms for a sample of white bread. The baseline shows very little disturbance near the acrylamide analyte due to the selective nature of the PCI with ammonia. The extracted concentration is approximately 34 ng/mL or 85 ng acrylamide per gram of white bread. Since acrylamide is formed when amino acids and sugars are heated together, it is logical to suspect the possibility of acrylamide formation in the inlet during injection. To test this possibility, the white bread extract was spiked with 100 ng of acrylamide and reanalyzed. The results calculated 135 ng/mL and suggest that either the relatively low temperature and short duration in the liner due to pressure pulsing mitigate acrylamide formation for this sample, or acrylamide formed in the inlet is highly reproducible. This may not be the case in all extracts or under all similar conditions.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0602EN.

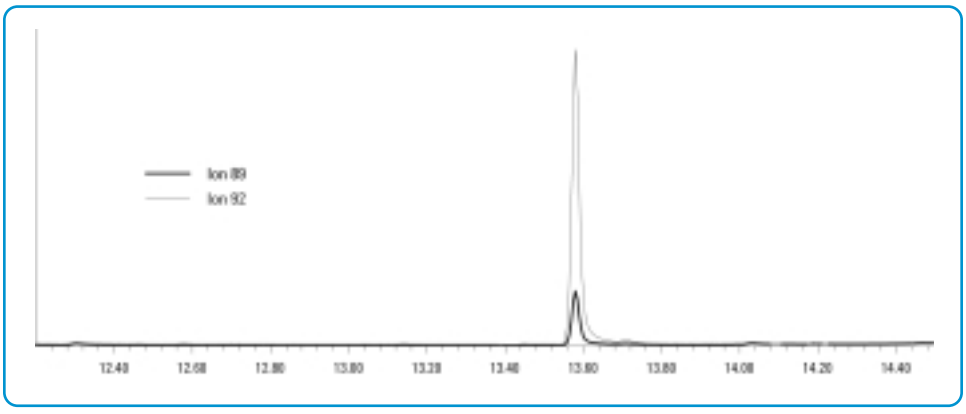


FIGURE 1. EXTRACTED ION CHROMATOGRAMS FOR ACRYLAMIDE (84 ng/g) IN SAMPLE OF WHITE BREAD.

Improving the Analysis of Fatty Acid Methyl Esters Using Retention Time Locked Methods and Retention Time Databases

The analysis of fatty acid methyl esters (FAMEs) is used for the characterization of the lipid fraction in foods and is one of the most important applications in food analysis. Lipids mainly consist of triglycerides, which are esters of one glycerol molecule and three fatty acids. Most edible fats and oils are composed largely of 12 to 20 carbon fatty acids [lauric acid (dodecanoic acid) to arachidic acid (eicosanoic acid)]. Besides linear saturated fatty acids, branched, mono-unsaturated, di-unsaturated, and higher unsaturated fatty acids can occur.

Two GC/MS methods are applicable for the analysis of FAMEs:

Method 1, using an Agilent DB-Wax column, is useful for the analysis of classical edible oils and fats, including the determination of butyric acid in milk fat.

Method 2, applying an Agilent DB-23 cyanopropyl column, can be used for the analysis of more complex samples, including fish oils and hydrogenated fats, for the determination of EPA and DHA and for *cis/trans* determination. Using retention time locking, GC/FID and GC/MS retention times can be closely matched for easy correlation of chromatograms between the instruments and RTL database searching makes peak identification more accurate.

The separation for a 37-component standard mixture on the 60-m x 0.25-mm id 0.15-µm DB-23 column using method 2 is shown in Figure 1. Using these conditions, all compounds in the standard mixture are resolved. Important to note is the separation of the *cis/trans* isomers and the separation of EPA (20:5, 19.15 min.) and DHA (22:6, 22.38 min.). This method is very useful for the analysis of fatty acid profiles in complex mixtures.

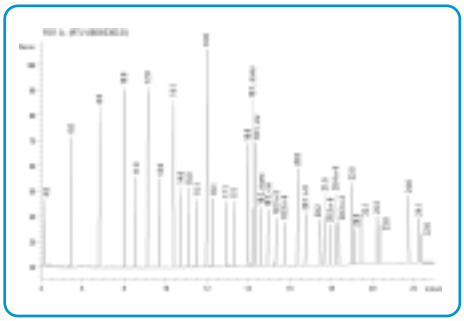


FIGURE 1. GC/FID ANALYSIS OF FAMES STANDARD MIXTURE ON A 60-M X 0.25-MM ID X 0.15-µM DB-23 COLUMN USING METHOD 2.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-5871EN.

The Analysis of Perchlorate by Ion Chromatography/Mass Spectrometry

Perchlorate is commonly used as an oxidant in solid fuel propellants for rockets and missiles. It has been found to be present in ground waters in California, Nevada and Arizona and in crops that use contaminated water for irrigation.

A method for the determination of perchlorate anion at sub-ppb levels using isocratic ion chromatography system (IC) and a single quadrupole mass spectrometer detector (MS) has been developed using an electrospray ionization (ESI) interface. The IC/MS method follows EPA Method 314 methodology originally developed for IC with conductivity detection at the single ppb range [1]. By using a set of instrument conditions chosen to reduce background interference and increase reliability, the IC/MS method is not affected by the addition of the interference matrix described in Method 314 on perchlorate recoveries throughout the measurable range. Typical recoveries are 90%-105% at the 0.5 and 1-ppb level in synthetic drinking and waste waters with the method detection limit (MDL) less than 100 ppt.

Figure 1 shows the chromatograms obtained from the analysis of perchlorate in lettuce. Note the lack of interferants around perchlorate. The "dip" in both the blank and spike lettuce samples is due to large amounts of another eluting material going through the electrospray source, suppressing the ionization of the background signal. Conventional conductivity detection is useless for this sample as the area around perchlorate elution is overwhelmed by large amounts of coeluting material.

The method also shows the feasibility and effectiveness of IC coupled to a quadrupole mass spectrometer in general. By using relatively simple method parameters and robust instrumentation, many of the difficulties previously seen with perchlorate analysis in complex matrices by IC/MS can be overcome.

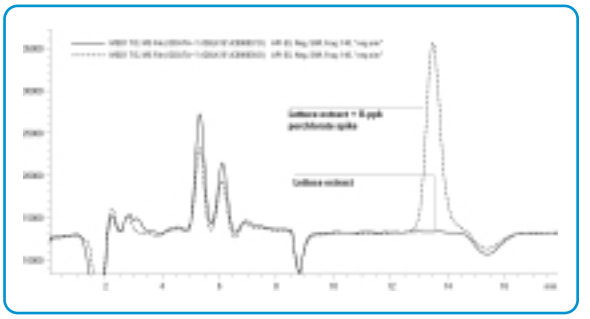


FIGURE 1. ANALYSIS OF A LETTUCE EXTRACT AND SPIKE.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0816EN.

References

[1] EPA METHOD 314.0, "Determination of Perchlorate in Drinking Water Using Ion Chromatography," Revision 1.0. November 1999, US EPA, Office of Ground Water and Drinking Water, publication 815-B-99-003, http://www.epa.gov/ogwdw/methods/met314.pdf

Pesticides

Most of the fruit and vegetables we put in our shopping bags are grown using pesticides – chemicals used to protect crops from insects and weeds. While it is important to ensure the food we eat is safe from disease and damage caused by insects, it is also vital for the protection of human health that pesticide residues are routinely monitored in food and water samples. Agilent's comprehensive range of chemical analysis instrumentation is used daily in food labs around the world to screen for pesticides to ensure that regulated Maximum Residue Levels (MRLs) are not exceeded. Analytical techniques are overwhelmingly based on chromatography (GC, LC), with detection by mass selective detectors.

Identification and Quantitation of Pesticides in the Parts-per-Trillion Range Using Retention Time Locking and GC/MS

Traditionally, pesticides are analyzed on a gas chromatograph (GC) with element-selective detectors (ESDs). Although these ESDs provide low ppb detection limits and are easy to operate, the data does not provide sufficient information to confirm a compound's presence with confidence. In contrast, a mass spectrometer (MS) provides additional information and increased confidence in the assignment of compound identity. In addition GC/MS detection limits can be optimized in various ways:

- Run the MS in single ion monitoring (SIM) mode
- Make large volume injections (LVIs)
- Combine both the above methods

Experimental

A mixture from the California Department of Food and Agriculture (CDFA) of 80 pesticides at 5000 pg/µL each was used as the stock solution for this study. The mixture containing carbamate, organochlorine, organophosphorus, and organonitrogen pesticides was used to compare the lowest detection limits of splitless injection and LVI under Scan and SIM modes.

LVIs in Combination with SIM Methods

By using LVI and SIM, samples at a concentration as low as 0.05 pg/µL can be quantified as shown in Figure 1. The top portion shows the chlorthal-dimethyl extracted ion chromatograms (EIC) of mass 299 and 301 from a 100-µL full-scan run. The bottom portion shows the same ions from a 100-µL SIM run. The SIM method shows better peak shape and lower baseline noise.

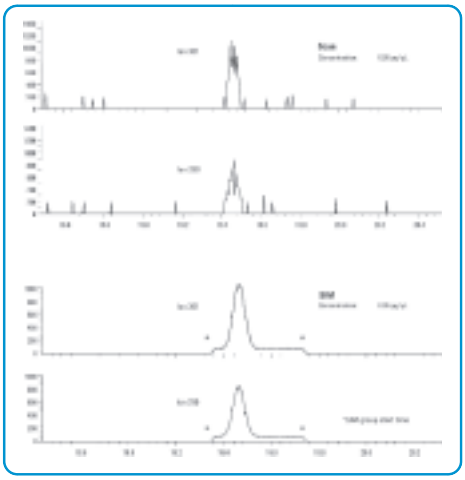


FIGURE 1. ION CHROMATOGRAMS OF 100-µL CHLORTHAL-DIMETHYL INJECTED AT 0.05 pg/µL. THE TOP PORTION WAS FROM A FULL-SCAN RUN, AND THE BOTTOM PORTION WAS FROM A SIM RUN.

The above example shows that both LVI and SIM are effective techniques to decrease the quantitation limit of target compounds from sub-ppm to ppt. Any lab can decrease the quantitation limit by a factor of 100 without any hardware modification. By adding LVI to the system, target compounds in femtogram/µL can be quantified.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-4392EN.

Trace Level Pesticide Analysis by GC/MS Using Large-Volume Injection

Concern has increased that certain pesticides and other synthetic chemicals may be acting as pseudo hormones which disrupt the normal function of the endocrine system in wildlife and humans. Because the endocrine system can be sensitive to extremely low hormone concentrations, there is a need to measure concentrations of suspected endocrine disrupters (many of which are pesticides) at very low legislated levels in food and water supplies. To achieve the required sensitivity, GC system detection limits can be improved by one to two orders of magnitude over standard methods that call for 1- or 2-µL injections using large-volume injection (LVI) with a programmable temperature vaporizer (PTV) inlet operating in solvent-vent mode.

Experimental

An Agilent 6890 Series gas chromatograph (GC), configured with a programmable temperature vaporizer (PTV) inlet, a 6890 Series automatic liquid sampler (ALS), and an Agilent 5973 mass selective detector (MSD), was used for the analysis of pesticides in standards and several food extracts. By making 100-µL injections, several pesticides could be identified by scanning gas chromatography/mass spectrometry (GC/MS) at the 100-ppt (100 ng/L) level (Figure 1).

Analysis of a bell pepper extract revealed several pesticide residues. As seen in Figure 2, chlorpyrifos and the endosulfans were easily detected. The Florida Department of Agriculture determined the concentration of chlorpyrifos, alpha-endosulfan, beta-endosulfan, and endosulfansulfate to be 0.210, 0.011, 0.018, and 0.013 ppm, respectively. It is important to note that these compounds could be detected with very high selectivity by extracting high mass ions that are characteristic of these pesticides but not of the matrix. Using LVI, there is ample signal from these less abundant ions for good quantitation.

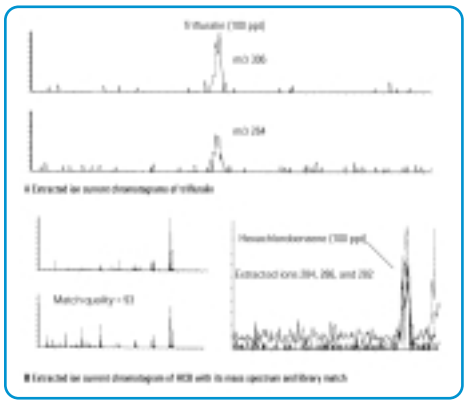


FIGURE 1. SCANNING GC/MS RESULTS FOR A PESTICIDE STANDARD CONTAINING TRIFLURALIN AND HEXACHLOROBENZENE AT 100 PPT. (TEN 10-µL INJECTIONS WERE MADE USING THE PTV INLET.)

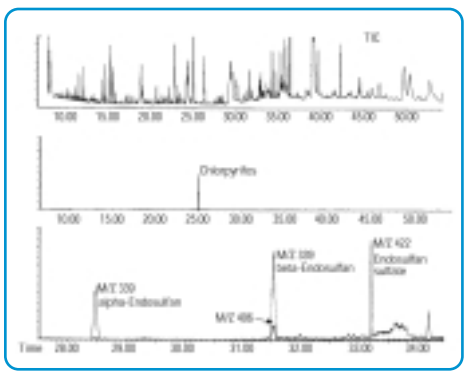


FIGURE 2. GC/MS ANALYSIS OF A BELL PEPPER EXTRACT. (TEN 10-µL INJECTIONS WERE MADE USING THE PTV INLET.)

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5966-1214E.

Routine Analysis of Trace Level Carbamate Pesticides in Food Using LC/MSD

The most often-used method for carbamate determination is the post-column derivatization technique using fluorescence detection. Drawbacks of this method include false positives due to lack of specificity, additional hardware and plumbing, and insufficient limits of detection. A more robust and routine alternative method uses LC/MS (quadrupole) with positive electrospray ionization to detect a mixture of nine analytes (Oxamyl, Methiocarbsulfoxide, Methiocarbsulfone, Aldicarb, Bendiocarb, Pirimicarb, Ethiofencarb, Fenobcarb, and Methiocarb) at low ppb levels without the derivatization step.

Matrix Effect and LOD

In many cases, the sample matrix interferes with the analyte responses. A selected ion monitoring (SIM) method collects less background signal compared to scan mode. Figure 1 shows the SIM chromatograms of 10-ppb carbamates in a broccoli extract. The injection was 5 µL on a 2.1-mm column. The percentage number in each parenthesis is the relative response of the analyte from the broccoli extract to the peak intensity from the analyte standard in methanol. Most of the analytes showed responses very similar (98% to 115%) to the standards, except Methiocarbsulfoxide, which had 71% of the response of the standard in methanol. The Limit of Detection (LOD) is defined as the sample concentration that produces a signal-to-noise (S/N) ratio of three in the broccoli extract. The LOD values of the nine carbamates are listed in Table 1.

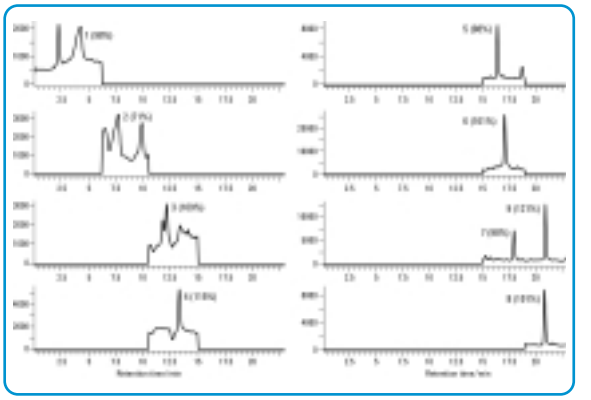


FIGURE 1. SIM CHROMATOGRAMS OF 10-PPB CARBAMATES IN BROCCOLI EXTRACT.

#	Compound	Base peak	Correlation coefficient (0.3—1000 ppb)	LOD (S/N = 3 in broccoli extract)
1	Oxamyl	237 $(M+NH_4)^+$	0.999	3 ppb
2	Methiocarbsulfoxide	242 $(M+H)^+$	0.999	10
3	Methiocarbsulfone	275 $(M+NH_4)^+$	0.999	10
4	Aldicarb	116 (fragment)	0.999	3
5	Bendiocarb	224 $(M+H)^+$	0.999	1
6	Pirimicarb	239 $(M+H)^+$	0.999	3
7	Ethiofencarb	226 $(M+H)^+$	0.999	3
8	Fenobcarb	208 $(M+H)^+$	0.998	1
9	Methiocarb	226 $(M+H)^+$	0.998	3

TABLE 1. CARBAMATES WITH THE BASE PEAK, CORRELATION COEFFICIENT AND LOD IN BROCCOLI EXTRACT.

Instrument detection limits were determined to be about 3 to 10 ppb for all the analytes in broccoli extract. The results demonstrate that the liquid chromatography with mass selective detection method is a viable technique to replace the nonspecific post-column derivatization process using fluorescence detection.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-4708EN.

Rapid Screening Method for the Analysis of Paraquat and Diquat by LC/MSD Using Selective Ion Monitoring and Large-Volume Injection

Paraquat and diquat, bipyridilium salts, are used in agriculture as nonselective-contact herbicides. They are also commonly used in commercial weed killer formulations for domestic weed control. Screening of these herbicides is possible using LC/MS and a direct aqueous injection of the sample.

The World Health Organization (WHO) has set an advisory value of 10 µg/L for paraquat in drinking water. In this application, a limit of detection (LOD) of well below 1 µg/L is achieved for paraquat and diquat, as well as for amitrole and chlormequat.

The method uses an ion-pairing reagent to help separate the compounds and to prepare the analyte as an ion. Typical ion-pairing reagents such as hexane-sulphonic acid are nonvolatile and cause the ion-pair complex to become nonvolatile. The ion-pair reagent used in this application is tridecafluoroheptanoic acid (TDFHA), which has been reported as suitable for the analysis of basic pesticides and sufficiently volatile for the electrospray interface [1].

Figures 1 and 2 show extracted ion chromatograms for diquat and paraquat, respectively, spiked into borehole water at a concentration of 1 µg/L. The method is capable of screening for the four herbicides with a run time of 20 minutes per sample.

No trace enrichment is required to obtain limits of detection below 1 µg/L with minimal sample preparation.

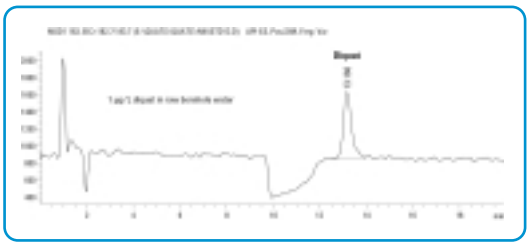


FIGURE 1. EXTRACTED ION CHROMATOGRAM OF 1 µg/L DIQUAT IN RAW BOREHOLE WATER.

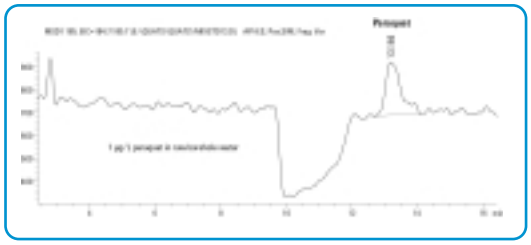


FIGURE 2. EXTRACTED ION CHROMATOGRAM OF 1 µg/L PARAQUAT IN RAW BOREHOLE WATER.

For more information on this topic, go to www.agilent.com/chem, click the library link and search forpub. # 5988-7220EN.

References

[1] Impact of Ion-pair Reagents on LC/MS Analysis. Agilent publication number 5968-8659E, 2000.

Use of Optional Gas and Collision Cell for Enhanced Sensitivity of the Organophosphorus Pesticides by GC-ICP-MS

Organophosphorus pesticides (OPs) are used widely as insecticides, herbicides, and fungicides. Concern over the levels of these compounds in our environment exists because they pose a threat to human health. As cholinesterase inhibitors, the OP pesticides are potent neurotoxins. A novel method has been developed using ICP-MS to detect phosphorous following separation of the OPs by GC.

Instrument Detection Limits

Table 1 depicts detection limits according to two EPA methods (columns 1,2) and by GC-ICP-MS (columns 3,4). A comparison of columns 1 and 3 demonstrates the superior sensitivity of GC-ICP-MS compared to conventional EPA methods.

Application to Water Samples

The U.S. EPA included diazinon, disulfoton, terbufos, and fonofos in Method 526. This method addresses concerns regarding the stability of these compounds in water. Ascorbic acid was used as a sample preservative to ensure the integrity of the sample. Samples analyzed in this work were extracted immediately after sampling and preservation. Additionally, samples were dechlorinated with sodium sulfite prior to extraction.

Tap water samples were collected in the laboratory and extracted in methylene chloride. The samples showed no organophosphorus pesticides above the method detection limit of 20 ppt. Moreover, duplicate samples were fortified with the compounds of interest, and recoveries ranged from 97% to 103%.

Analyte	Instrument LOD of U.S.EPA Method 507	Instrument LOD of U.S.EPA Method 526	Instrument LOD calculated as per U.S.EPA	LOD for ICP-MS calculated as per IUPAC
Diazinon	26 ppb	30 ppb	0.2 ppb	0.012 ppb
Disulfoton	5.8 ppb	50 ppb	0.2 ppb	0.004 ppb
Terbufos	11 ppb	50 ppb	0.2 ppb	0.004 ppb
Fonofos	—	60 ppb	0.2 ppb	0.007 ppb

TABLE 1. INSTRUMENT DETECTION LIMITS FOR ORGANOPHOSPHORUS PESTICIDES.

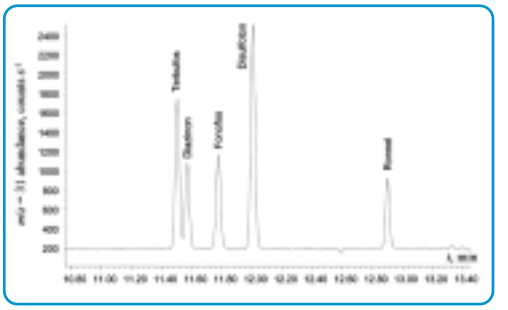


FIGURE 1. CHROMATOGRAM OF 10 PPB OF DIAZINON AND FONOFOS, 20 PPB OF TERBUFOS AND 30 PPB OF DISULFOTON OBTAINED UNDER OPTIMAL GC-ICP-MS CONDITIONS.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-9317EN.

Veterinary Drugs

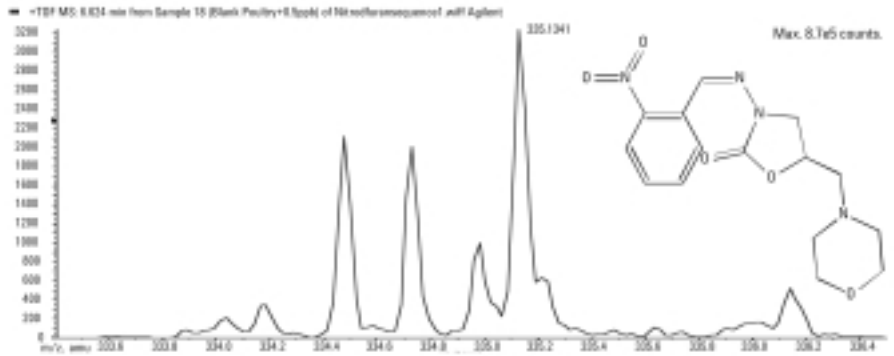
Animal diseases caused by viruses, bacteria, protozoa, and/or fungi are prevented or treated with drugs. It is also common practice to administer growth-enhancing drugs to livestock and poultry during their lifetime. Because drug residues may be found in foods of animal origin such as milk, eggs, and meat, government agencies around the world implement strict surveillance and monitoring programs to ensure food safety. Agilent's advanced technologies and methodologies based on mass spectrometry are highly suitable for the rapid and reliable analysis of drug residues in foods at regulated levels.

High-Resolution Quantitative Analysis of Nitrofuran Derivatives in Poultry and Shrimp Using a New oa-ESI-TOF

The drugs furazolidone, furaltadone, nitrofurazone, and nitrofurantoin belong to a group of nitrofuran antibacterial drugs which are widely used as feed additives to prevent bacterial enteritis, Escherichia coli, and Salmonella infections in cattle, fish, swine, and poultry.

Time-of-Flight (TOF) mass spectrometry is well known for its high resolution and accurate mass-measurement capabilities. The high-resolving power enables good mass-measurement accuracy and the differentiation of isobaric species, i.e., two compounds with the same nominal mass but different elemental composition and, therefore, different exact masses.

Operating the time-of-flight (TOF) mass spectrometer with a dual orthogonal electrospray source in positive ion mode provides fully automated, accurate mass assignments in the low ppm range with wide dynamic range for nitrofuran metabolites. The method allows quantitation of nitrofuran antibiotics down to 0.5 ppb in shrimp (Figure 1) and poultry with very good relative standard deviations. Mass accuracy is maintained throughout the concentration range with standard deviations less than 1 ppm. Internal referencing through a dual orthogonal ESI sprayer design ensures routine operation.



	Formula	Calculated m/z (amu)	mDa Error	PPM Error	DBE
1	C15 H19 N4 O5	335.1349	-0.3964	-1.1828	8.5
2	C14 H23 O9	335.1336	0.9488	2.8075	3.5

FIGURE 1. MH^+ REGION FOR NPAMOZ AT THE 0.5 PPB LEVEL IN SHRIMP WITH EMPIRICAL FORMULA CALCULATION RESULTS.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-1302EN.

Quantitation of Nitrofuran Metabolites in Shrimp and Poultry by LC/MS/MS Using the LC/MSD Trap XCT

Nitrofuran antibiotics are widely used for the treatment of infectious diseases in cattle, pigs, shrimp, and poultry. Due to their rapid metabolism, nitrofuran parent substances are not suitable for monitoring, and typically their metabolites are analyzed. An LC/MS/MS method exists for the qualitative and quantitative measurement of nitrofuran metabolites in chicken and shrimp, using an ion trap with an orthogonal electrospray source in positive ion mode and multiple reaction monitoring (MRM).

Very low limits of detection (LOD) are required for nitrofuran metabolites, and the metabolite derivatization method increased the ionization efficiency, as well as improved the chromatographic separation. Operating the ion trap mass spectrometer in MRM mode, only precursor ions are chosen and full-scan MS/MS-spectra of the corresponding analytes are acquired. These full-scan MS/MS spectra are then used for identification by comparing them with MS/MS spectra stored in a library. No further qualifier ion has to be monitored.

The European Union has set a Minimum Required Performance Level (MRPL) of 1 µg/kg for Nitrofuran metabolites. These detection limits are easily reached using this method with LOQs ranging from 0.125 µg/kg for NBA-AMOZ to 0.25 µg/kg for NBA-AOZ and NBA-SEM, and 0.5 µg/kg for NBA-ADH. See Figure 1.

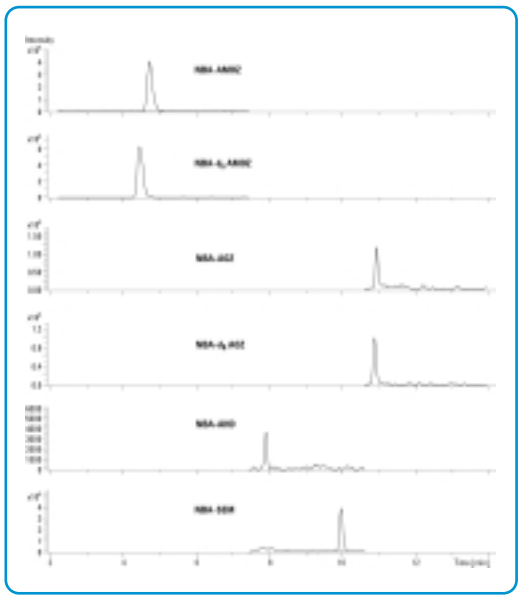


FIGURE 1. REPRESENTATIVE CHROMATOGRAM OF A POSITIVE SHRIMP SAMPLE AT A LEVEL OF 0.25 µg/Kg.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0738EN.

A Validated Atmospheric Pressure Chemical Ionization Method for Analyzing Sulfonamides in Pork Muscle

Meat, edible organs, animal feed, and animal waste may contain antibiotics, growth hormones, and other chemicals that can enter the food supply chain. The result of low-level exposure of these compounds to humans, some health specialists warn, is there may be reduced options for effectively treating disease with antibiotics, such as penicillin and sulfa drugs, as antibiotic-resistant strains of bacteria may develop. One example of broad-spectrum antimicrobials used in both humans and animals includes sulfonamides.

A fast and sensitive method using Atmospheric Pressure Chemical Ionization (APCI) LC/MS (quadrupole) has been developed and validated for the analysis of sulfonamide antibiotic residues in pork muscle. Samples were extracted with acidified methanol, centrifuged, and a portion of the extract was diluted with water. This dilution was analyzed directly by the LC/MS, with all compounds eluting in less than 5 minutes. The DL ranged from 10 to 25 ng/g of tissue.

If greater sensitivity is required, a solid-phase extraction (SPE) cleanup step can be introduced to remove the majority of co-extracted materials, allowing for a more concentrated final extract and DLs in the range 4 to 13 ng/g. SPE also results in a simpler chromatogram for integration and interpretation, but is more costly and time consuming than simple dilution.

Compound Identification and Confirmation

The Agilent 1100 MSD has the capability of acquiring up to four separate MS signals during the same run, where each signal can be made up of a number of selected ions (SIM) or a full-scan spectrum. For example, Signal 1, with a low fragmentor voltage to maximize parent-ion response, can include each of the $[M+H]^+$ ions in the target list, while Signal 2, at higher fragmentor voltages, can acquire the confirmatory fragment ions. For analytes expected at higher concentrations, Signal 1 could acquire in SIM mode for quantitation, while Signal 2 could be set for scan mode for identification. Figure 1 demonstrates the former example, with the Fragmentor set to 70 V for Signal 1 (MSD1), and 200 V for Signal 2 (MSD2).

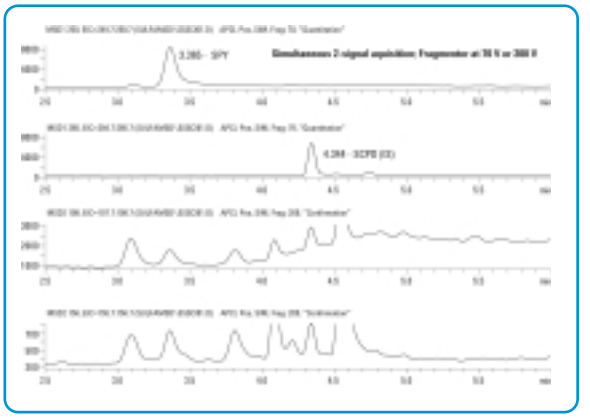


FIGURE 1. DUAL MSD ACQUISITION SIGNALS (MASSES 108 AND 156 ARE CLASS-SPECIFIC FRAGMENTS FOR SULFONAMIDES).

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0182EN.

Detection, Confirmation and Quantification of Chloramphenicol in Honey and Shrimp at Regulatory Levels Using Quadrupole and Ion Trap LC/MS

Chloramphenicol (CAP) is a broad-range antibiotic that has found its way into foodstuffs, such as honey and shrimp. Because it has displayed significant toxicological effects on humans, it has been banned from foods in the European community and the United States at levels greater than 0.1 ppb. Methodology capable of meeting these regulatory requirements has been developed based on quadrupole (with negative mode electrospray ionization) and ion trap LC/MS. The quadrupole instrument provides excellent results for quantitative analysis and can give some confirmation information. The ion trap system gives excellent full-spectrum confirmation at the regulated concentration.

Analysis of Honey and Shrimp
Samples of the two foodstuffs that were known to contain CAP were extracted using a simple liquid-liquid extraction procedure using ISOLUTE HM-N cartridges prior to analysis by both instruments. Sample results for the honey and shrimp samples obtained with the quadrupole and trap MSD are compared (Figures 1 and 2).

The LOD for the honey and shrimp samples varies between detectors. Both instruments provide a limit of detection at or below 0.1 ppb in both sample types. Detection limits are lower using the ion trap for shrimp because of less matrix interference.

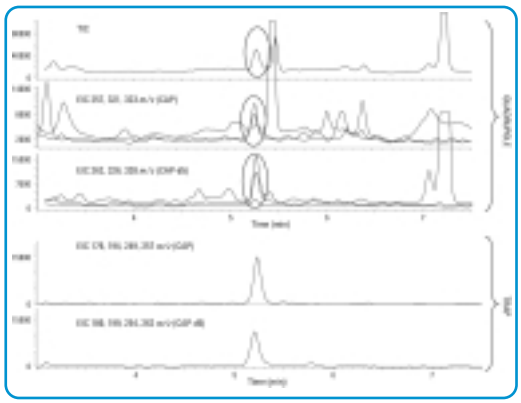


FIGURE 1. ANALYSIS OF A HONEY SAMPLE CONTAINING 0.5 PPB CAP AND 1 PPB CAP-D5.

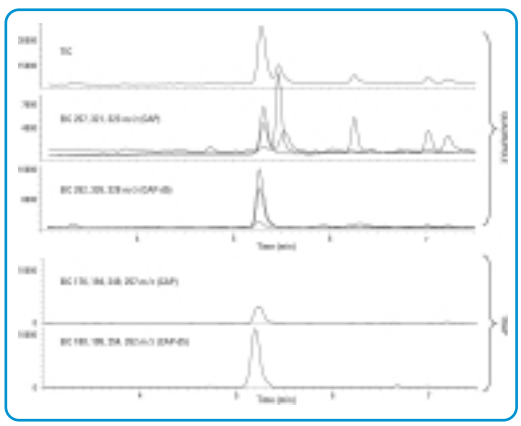


FIGURE 2. ANALYSIS OF A SHRIMP CONTAINING 0.35 PPB CAP AND 1 PPB CAP-D5.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-9920EN.

The Analysis of Fluoroquinolones in Beef Kidney Using HPLC Electrospray Mass Spectrometry

Fluoroquinolones are synthetic antibacterial compounds derived from nalidixic acid, used to treat animal infections that are resistant to other antibacterial agents. They have a broad spectrum of activity, acting against both gram-positive and gram-negative bacteria. The maximum residue limit (MRL) for enrofloxacin (as the sum of enrofloxacin and ciprofloxacin) for kidney is 200 µg/kg in bovine and ovine species, and 300 µg/kg for porcine, poultry, and rabbits. For all other food-producing species, the MRL is 200 µg/kg in kidney [1].

A fast and simple screening method has been validated for the analysis of three fluoroquinolone antibiotics (ciprofloxacin, enrofloxacin, and sarafloxacin) in beef kidney. Samples were extracted with acidified methanol, centrifuged, diluted with water, and filtered. The diluted extract was analyzed directly by LC/MS (quadrupole) using electrospray ionization (ESI) in positive ion mode.

The chromatograms in Figure 1 compare the blank beef kidney sample to a sample fortified at 33 µg/kg. In each case, the selected ions are the protonated forms of the parent ion, as well as the protonated ions resulting from the loss of H_2O (M-18) and CO_2 (M-44).

Using an internal standard, mean recoveries were 73%–96% at spiking levels of 33 µg/kg (ppb), with statistically derived detection limits of 8–19 µg/kg. This is below the European Union maximum residue limit of 200 µg/kg for enrofloxacin and ciprofloxacin in bovine kidney.

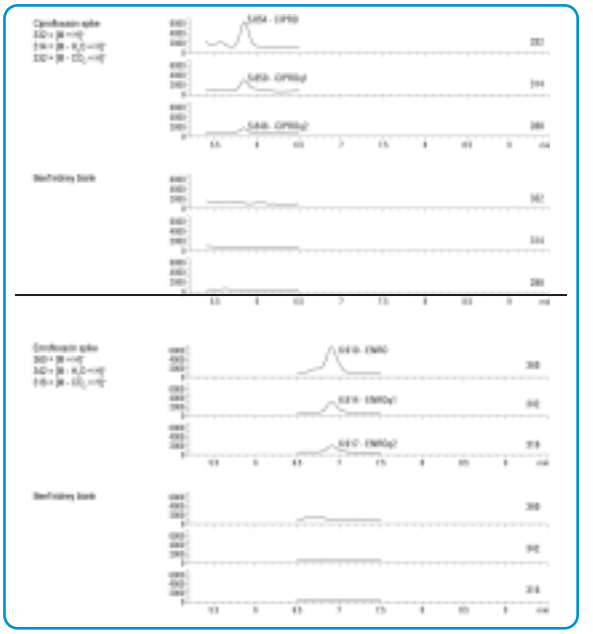


FIGURE 1. COMPARATIVE EXTRACTED ION CHROMATOGRAMS FOR FLUOROQUINOLONES SPIKED INTO BEEF KIDNEY.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0596EN.

References

[1] The European Agency for the Evaluation of Medicinal Products, Veterinary Medicines and Inspections, EMEA/MRL/820/02-FINAL, January 2002.

Packaging

The packaging used to present and protect foodstuffs is essential to keeping food fresh. However, additives for the manufacturing process can unintentionally migrate into foods from packaging materials. These are permitted only if the amounts present are so low as to be considered insignificant. Direct additives are intentionally added to foods to perform a specific function. Examples include preservatives, colorings, and flavorings. Used principally to improve and maintain food quality, all additives must be proven to be safe, effective, and measurable before being allowed in the foods we consume. Most countries' food-additive legislation is based on a positive list, with only authorized substances permitted for use and in limited quantities. Agilent's portfolio of instrumentation and applications expertise provides food scientists with the tools they need to meet their analytical challenges.

GC/MS Approaches to the Analysis of Monochloropropanediol

Hydrolyzed vegetable protein (HVP) is a widely used flavoring found in soups, sauces, and some meat products. During the acid hydrolysis process of vegetable proteins, the hydrochloric acid agent reacts with triglycerides to produce the suspected carcinogen 3-chloro-1,2-propanediol (3-MCPD) [1]. The Association of Official Analytical Chemists (AOAC) has published a method for the extraction, separation and identification of 3-MCPD in foods and ingredients, using electron impact (EI) ionization GC/MS [2]. The 3-MCPD is eluted with diethyl ether and a portion is derivatized with heptafluorobutyrylimidazole. The resulting EI mass spectrum lacks a molecular ion and has a base peak at *m/z* 169 from $[C_3F_7]^+$ fragments; see Figure 1. However, selected ion monitoring (SIM) of *m/z* fragments at 453, 289, 275, and 253 in a standard solution suggests detection at subpicogram levels is possible.

The methodology can be improved further using electron capture negative ionization (ECNI) GC/MS. Figure 2 shows the ECNI mass spectrum of the 3-MCPD derivative under standard conditions with methane buffer gas. Unlike the EI results, the molecular ion (502 *m/z*) is detected, although at low relative intensity. Analysis of standards suggests that it would be possible to detect a few picograms in the scanning mode and less than one picogram in the selected ion mode (SIM).

Further optimization of ECNI is possible, such as a lower source temperature to take advantage of the low boiling point of the derivative, which may improve the spectrum and detection limits. The real advantage, though, is expected to be in typical food samples where its greater selectivity will demonstrate a strong suppression of chemical noise and enhance method detection limits.

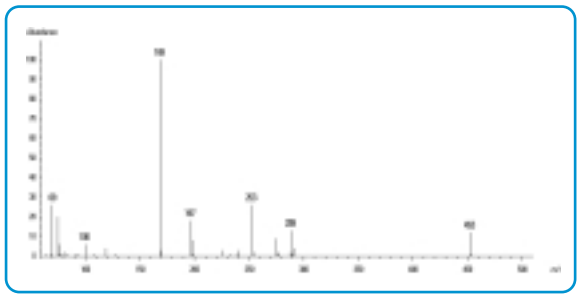


FIGURE 1. ELECTRON IMPACT IONIZATION MASS SPECTRUM OF THE 3-MCPD HEPTAFLUOROBUTYRYL DERIVATIVE AT 70 EV FOR THE 60 TO 510 M/Z MASS RANGE. THE MOLECULAR ION [M]+ WOULD BE EXPECTED AT 502 M/Z.

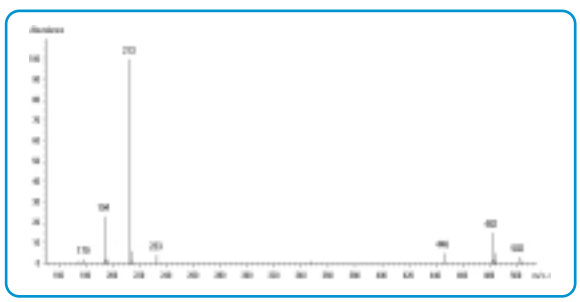


FIGURE 2. ELECTRON CAPTURE NEGATIVE ION (ECNI) CHEMICAL IONIZATION MASS SPECTRUM OF DERIVATIZED 3-MCPD WITH METHANE BUFFER GAS FROM 150 TO 510 *M/Z*. NOTE THE PRESENCE OF THE MOLECULAR ANION [M]- NOT SEEN IN EI.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-4287EN.

References

[1] *Reports of the Scientific Committee for Food, Food Sciences and Techniques*, 36th Series, European Commission, Luxembourg, Belgium.

[2] Brereton, P., et al., Determination of 3-chloro-1,2-propanediol in foods and food ingredients by gas chromatography with mass spectrometric detection: Collaborative study. *Journal of the AOAC International*, 2001. 84(2): p. 455-465.

A New Approach to the Analysis of Phthalate Esters by GC/MS

Some phthalate esters are characterized as endocrine disruptors capable of liver and kidney damage, and possible testicular or reproductive-tract birth defect problems. GC/MS methodology using positive chemical ionization (PCI) and retention time locking exists for the determination of 29 phthalate esters, including six recently banned from baby toys by the European Union [1], in a wide variety of matrices. Using ammonia as the PCI reagent gas provides a high degree of selective ionization for the phthalates, primarily producing spectra in which the protonated molecule (M+1) is the base peak. PCI is also an advantage in complex matrices, where the non-selective ionization of Electron Impact (EI) ionization produces a high chemical background. The chromatograms presented in Figure 1 illustrate this point. The EI spectra of the phthalates produce *m/z* 149 as the base peak for all the phthalates present; distinguishing ions are minor constituents (<10% relative intensity), making identification complicated. However, by examining the appropriate PCI-ammonia ions, the various phthalates are easily distinguished.

"Locking" the retention time enhances confidence in the characterization of the various phthalate isomers on the basis of their definitive retention time. This is especially helpful for determinations using selected ion monitoring (SIM), since SIM groups need not be edited after column maintenance [2].

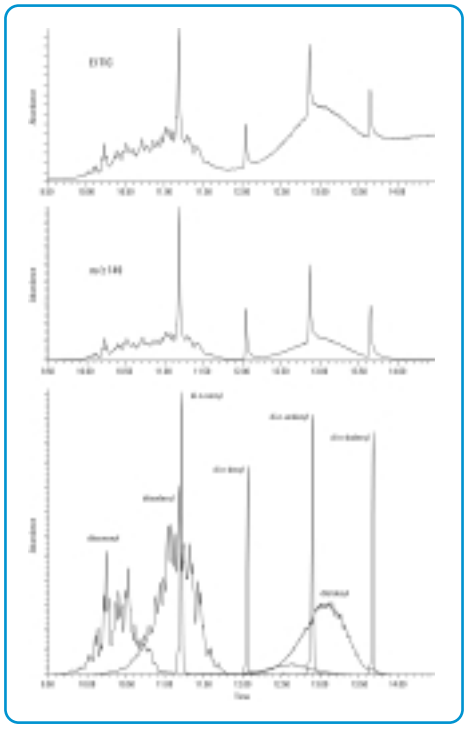


FIGURE 1. CHROMATOGRAMS OF DINONYL, DIISONONYL, DIDECYL, DIISODECYL, DIUNDECYL, DIDODECYL, DITRIDECYL PHTHALATE ESTERS IN EI (UPPER PANEL), EI AS AN EXTRACTED ION CHROMATOGRAM AT *M/Z* 149 (MIDDLE PANEL), AND PCI-EXTRACTED ION CHROMATOGRAM WITH IONS SELECTED FOR INDIVIDUAL PHTHALATE CLASSES. THE EI INFORMATION IS INSUFFICIENT TO IDENTIFY COELUTING PHTHALATES. FOR EXAMPLE, THE DINONYL AND DIUNDECYL PHTHALATES ARE "BURIED UNDER" THE SIGNALS FROM THE ISODECYL AND DITRIDECYL PHTHALATES.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-2244EN.

References

[1] *Official Journal of the European Communities, Decision 198/815/EC.* 1999, European Commission; European Union Scientific Committee on Toxicology, Ecotoxicology, and the Environment.

[2] *Prest, H. and P. Cormia, Retention Time Locking: Advantages in GC/MS SIM Analysis.* 1999, Publication number (23) 5967-3797E, Agilent Technologies.

Analysis of Chemical Coatings (BADGE) in Food Product Extracts by LC/MS

Bisphenol A diglycidyl-ether (BADGE) is used in the three most common food-can coatings (organosol lacquer, epoxy lacquer, and polyester lacquer) to improve high-temperature stability and to remove the hydrochloric acid that forms during the curing process. In canned food containing fat, BADGE migrates into the fatty phase where it is stable, whereas in water it is hydrolyzed. A maximum concentration of 1 mg BADGE per kg of food is allowed.

An easy, reliable method has been developed using LC/MSD with electrospray ionization (ESI) to investigate the migration of BADGE into fat and oil containing canned fish products and to determine whether BADGE residuals meet food-packaging regulations.

A BADGE standard of 1.09 ng/µL was analyzed to obtain a mass spectrum. Figure 1 shows the diode-array detector (DAD) was not sufficiently sensitive to determine this amount of compound. The analysis was repeated using a 1 uL injection of sardine and tuna extracts. (Figures 2 and 3) at 20 ppm and 0.2 ppm respectively. Selected ion monitoring (SIM) mode was used to obtain the best sensitivity for the quantitation. Using SIM, BADGE was easily detected in both extracts.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5967-6102E.

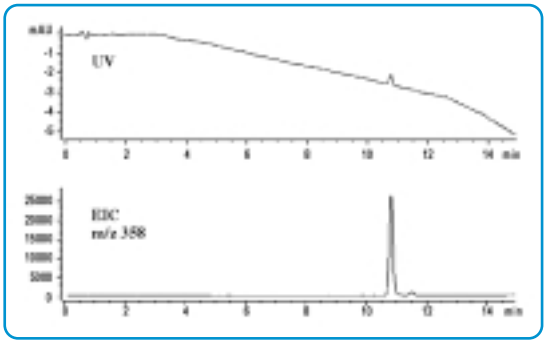


FIGURE 1. LC/MS ANALYSIS OF BADGE.

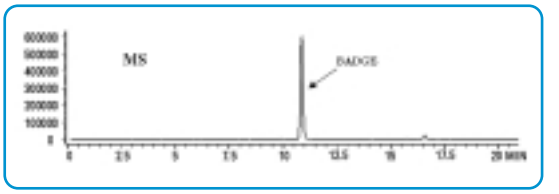


FIGURE 2. ANALYSIS OF 20 PPM BADGE IN SARDINE EXTRACT.

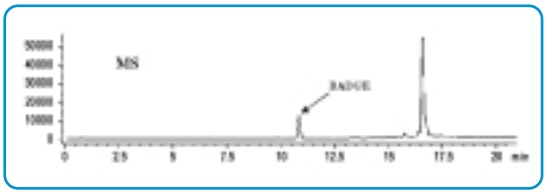


FIGURE 3. ANALYSIS OF 0.2 PPM BADGE IN TUNA EXTRACT.

Metals

Analysis of metals in foods is critical. While metals such as Zn, Cu, Ca, Mg, Fe, Se, Li, Co, Mn, and P are important nutrients required for human and animal health, other metals including Pb, Cd, As, Be, Ni, and Hg have no known nutritional function and may be highly toxic, even at very low concentrations. Many metals have nutritional functions at low concentrations and are toxic at higher concentrations. The nutritional value or toxicity of metals is also dependent on the form or species of the metal. Agilent's highly sensitive ICP-MS series of instruments and leadership in coupling chromatographic techniques to ICP-MS provide food labs with the analytical tools they can rely on.

A Comparison of the Relative Cost and Productivity of Traditional Metals Analysis Techniques Versus ICP-MS in the Analysis of Foods

As our understanding of the effects of metals on human and animal health increases, we find it necessary to monitor more elements in more types of samples at lower levels than ever before. The challenge is to implement suitable techniques capable of cost-effective and high-quality analytical measurement of a full range of elements in a variety of sample types.

Traditionally, elemental analysis in foods has been performed by atomic absorption and atomic emission spectroscopy. The trace elements have generally been measured by graphite furnace atomic absorption (GFAA), a highly sensitive single-element technique. The more common elements have been measured by inductively coupled plasma optical emission spectroscopy (ICP-OES), which is less sensitive but capable of simultaneous multi-element analysis. However, as the need for more analyses at lower detection limits increases, the combination of GFAA plus ICP-OES is not up to the task, and many labs are investing in ICP-MS for the analysis of all metals in foods and drugs.

A spreadsheet-based sample cost-comparison model developed in Excel showed that for almost any metals laboratory, analyzing at least 100 samples per week (400 per month) and using a combination of GFAA and ICP-OES for the analysis, converting to ICP-MS will save money; see Figure 1. Depending on the number of samples, the payback for the ICP-MS can be as short as a few months. The cost advantages are not reduced significantly even if the laboratory already owns its GFAA and ICP-OES instruments. They are also not significantly affected by the number of GFAA elements.

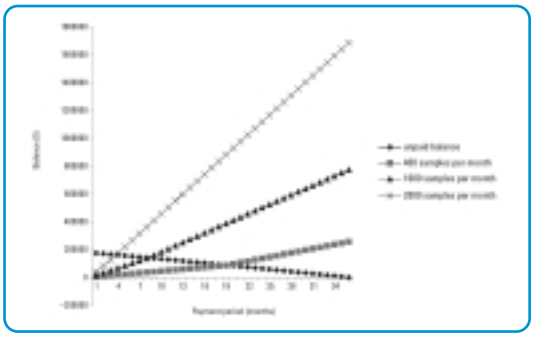


FIGURE 1. SHOWING CUMULATIVE SAVINGS PER MONTH FOR THREE SAMPLE LOADS; 400, 1000, AND 2000 SAMPLES PER MONTH VERSUS BALANCE DUE ON LOAN.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-1585EN.

Determination of Mercury in Microwave Digests of Foodstuffs by ICP-MS

The determination of sub ng/g concentrations of mercury is of special importance in the field of trace metal analysis. Even at trace levels, mercury is toxic and causes neurological damage, particularly in fetuses and young children. Anthropogenic sources of mercury in the environment include coal-fired power stations and chlor-alkali works. In the aquatic environment, bacteria convert elemental mercury Hg(0) to methylmercury, which is accumulated and passed up the food chain. Fish and shellfish are significant contributors of mercury to the human diet.

Mercury is recognized as a problem element analytically. It is known to adsorb onto the walls of storage containers and volatilize as mercury vapor. Additionally, its high first ionization potential and numerous isotopes have limited its sensitivity in ICP-MS analysis. However, a quantitative method for the determination of mercury in foodstuffs is available using a 7500 ICP-MS. Microwave digests were prepared and then analyzed by ICP-MS equipped with the integrated sample introduction system (ISIS) in the high sample throughput mode, and a microflow concentric nebulizer. To avoid memory effects, gold was added offline to all standards/samples and wash solutions to act as a cleansing agent. Five calibration plots over a 36-hour period are shown in Figure 1 to demonstrate the system's stability. As can be seen, good linearity was achieved over an extended calibration range, indicating that memory effects had been effectively eliminated. Between the calibrations, more than 120 various microwave foodstuff digests were analyzed.

Two certified reference materials (CRMs) were analyzed throughout a survey of 500 samples. These acted as quality control materials for the microwave digestion as well as the quantification. The CRMs used were a crab paste – Metals LGC 7160, 0.096 mg/kg and peach leaves – NIST 1547, 0.031 mg/kg. Each CRM was analyzed 14 times on different runs during a survey over a one-month period. The results can be seen in Figure 2.

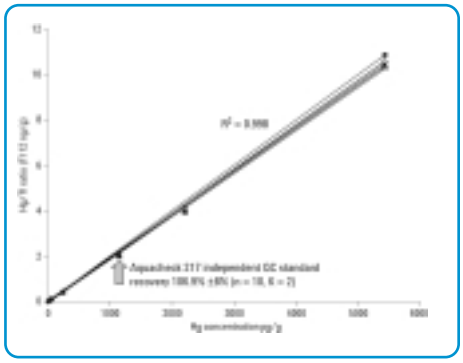


FIGURE 1. CALIBRATIONS OVER 36 HOURS OF CONTINUOUS OPERATION.

This method proved robust for the analysis of foodstuffs for mercury, in runs lasting in excess of 36 hours without loss of sensitivity or stability. The sensitivity of the 7500 ICP-MS gives method detection limits at low ppt levels in the foodstuff digests. The extended calibration range reduces the need for dilutions and reruns.

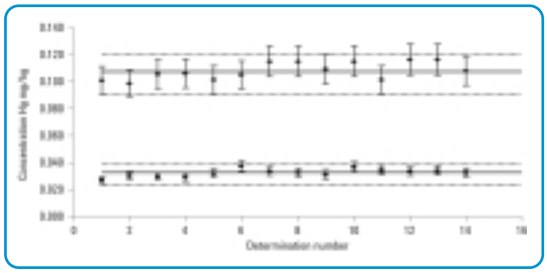


FIGURE 2. NIST 1547 PEACH LEAVES (BOTTOM TRACE) AND LGC 7160 CRAB PASTE (TOP TRACE) WERE ANALYZED 14 TIMES OVER A PERIOD OF ONE MONTH. EACH POINT REPRESENTS A SEPARATE DIGEST. LGC 7160 CERTIFIED VALUE 0.096 = ±0.108 mg/Kg, NIST 1547 CERTIFIED VALUE 0.031 = ±0.007 mg/Kg.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5989-0027EN.

Measuring Traces in Milk Powder

With legislation covering many different food types, most food laboratories need to analyze large numbers of samples annually. Robust inductively coupled plasma mass spectrometry (ICP-MS) instrumentation provides rapid multi-element analysis at trace levels, breaking the bottleneck created by older, slower techniques such as graphite furnace atomic absorption spectroscopy (GFAAS).

Table 1 summarizes the analysis of NIST 1549 Milk Powder using an Agilent 7500a ICP-MS instrument. The milk powder was digested using a standard method in a microwave digestion system, diluted in 0.1% nitric acid and analyzed with five replicate measurements. Concentration data was calculated using external calibration in 0.1% nitric acid. With the exception of Se, which is subject to interferences from argon and chloride in the plasma and sample matrix, recoveries are excellent.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-6795EN.

Element	Found (mg/kg)	Certified (mg/kg)	%RSD
Mn	0.26	0.26	1.3%
Cu	0.69	0.70	1.1%
Zn	48	46	0.2%
Se	0.19	0.11	9.1%
Pb	0.020	0.019	3.0%

TABLE 1. ANALYSIS OF NIST 1549 MILK POWDER USING AN AGILENT 7500a

NIST 1573 Tomato Leaves using an Agilent 7500 ORS ICP-MS

In extracts of complex matrices such as foods, traditional (non-cell) ICP-MS can suffer from interferences. Though they are less severe than with traditional techniques, e.g., ICP-atomic emission spectroscopy (AES), they can compromise detection limits for certain key elements; see Table 1. The 7500 Octopole Reaction System (ORS) ICP-MS can eliminate these interferences, allowing for trace measurement even in difficult matrices. The data in Table 2 was obtained from the analysis of a perchloric/nitric acid digestion of NIST 1573 Tomato Leaves using an Agilent 7500c ORS instrument. The excellent agreement between the reference and obtained values for Cr, Fe, and As for multiple isotopes illustrates how the ORS eliminates interferences from ArC, ArO, and ArCl. The data was obtained in a single acquisition highlighting the wide dynamic range of the 7500 Series.

For more information on this topic, go to www.agilent.com/chem, click the library link and search for pub. # 5988-6795EN.

Element	Molecular Interference	Element	Molecular Interference
Cr	$^{40}Ar^{12}C$, $^{38}Ar^{16}O$	Cu	$^{40}Ar^{23}Na$
V	$^{35}Cl^{16}O$	As	$^{40}Ar^{35}Cl$
Fe	$^{40}Ar^{16}O$	Se	$^{40}Ar^{37}Cl$, $^{40}Ar^{38}Ar$, $^{40}Ar^{40}Ar$

TABLE 1. TYPICAL INTERFERENCES IN BIOLOGICAL/CLINICAL MATRICES.

Element	Certified (mg/kg)	Found (mg/kg)	Element	Element	Element
43Ca	5.05%	5.08%	63Cu	4.7	4.4
39K	2.70%	2.62%	65Cu	4.7	4.4
52Cr	1.99	1.79	75As	0.112	0.115
53Cr	1.99	1.79	78Se	0.054	0.06
54Fe	368	368	111Cd	1.52	Se
56Fe	368	368			1.42

TABLE 2. ANALYSIS OF NIST 1573 TOMATO LEAVES USING THE 7500 ORS.

Agilent Pesticide Library

Pesticide identification is efficient and certain with Agilent's GC/MS instrumentation, retention time locking (RTL) software tool, and RTL pesticide library of 567 compounds, as listed below. Each entry in the RTL library has a full spectrum and a target retention time. When the sample is run on an Agilent GC/MS system for confirmation, RTL will ensure that the analytes appear at the same retention times consistently. The match or mismatch of the retention times with the library entries can be used as a qualifier, adding another level of confidence in the results.

Note: *The pesticide library can be updated by the user at any time.*

No.	Compound name	CAS #
1	1,2,4-Trichlorobenzene	120-82-1
2	1,2-Dibromo-3-chloropropane	96-12-8
3	17a-Ethynylestradiol	57-63-6
4	2-(1-naphthyl)acetamide	86-86-2
5	2-(2-Butoxyethoxy)ethyl thiocy	112-56-1
6	2-(Octylthio)ethanol	3547-33-9
7	2,3,4,5-Tetrachlorophenol	4901-51-3
8	2,3,4,6-Tetrachlorophenol	58-90-2
9	2,3,5,6-Tetrachlorophenol	935-95-5
10	2,3,5-Trichlorophenol	933-78-8
11	2,3,5-Trimethacarb	2655-15-4
12	2,3,5-Trimethylphenyl methyl c	2655-15-4
13	2,3,7,8-Tetrachlorodibenzofura	51207-31-9
14	2,3,7,8-Tetrachlorodibenzo-p-d	1746-01-6
15	2,4,5-T methyl ester	1928-37-6
16	2,4,5-Trichlorophenol	95-95-4
17	2,4,6-Trichlorophenol	88-06-2
18	2,4-D methyl ester	1928-38-7
19	2,4-D sec-butyl ester	N/A
20	2,4-DB methyl ester	18625-12-2
21	2,4-Dichlorophenol	120-83-2
22	2,4-Dichlorophenyl benzenesulf	97-16-5
23	2,4-Dimethylaniline	95-68-1
24	2,6-Dichlorobenzonitrile	1194-65-6
25	2,6-Dimethylaniline	87-62-7
26	2-[3-Chlorophenoxy]propionamid	5825-87-6
27	2-Ethyl-1,3-hexanediol	94-96-2
28	2-Hydroxyestradiol	362-05-0
29	2-Methylphenol	95-48-7
30	2-Phenoxypropionic acid	940-31-8
31	3,4,5-Trimethacarb	2686-99-9
32	3,4-Dichloroaniline	95-76-1
33	3,5-Dichloroaniline	626-43-7
34	3-Chloroaniline	108-42-9
35	3-Hydroxycarbofuran	16655-82-6
36	4,4'-Dichlorobenzophenone	90-98-2
37	4,6-Dinitro-o-cresol (DNOC)	534-52-1
38	4-Chloroaniline	106-47-8
39	4-Methylphenol	106-44-5

No.	Compound name	CAS #
40	5,7-Dihydroxy-4'-methoxyisofla	491-80-5
41	9,10-Anthraquinone	84-65-1
42	Acephate	30560-19-1
43	Acetochlor	34256-82-1
44	Acifluorfen methyl ester	N/A
45	Alachlor	15972-60-8
46	Aldrin	309-00-2
47	Allidochlor	93-71-0
48	Ametryn	834-12-8
49	Amidithion	919-76-6
50	Aminocarb	2032-59-9
51	Amitraz	33089-61-1
52	Ancymidol	12771-68-5
53	Anilazine	101-05-3
54	Aniline	62-53-3
55	Atraton	1610-17-9
56	Atrazine	1912-24-9
57	Azaconazole	60207-31-0
58	Azamethiphos	35575-96-3
59	Azinphos-ethyl	2642-71-9
60	Azinphos-methyl	86-50-0
61	Aziprotryne	4658-28-0
62	Azobenzene	103-33-3
63	Barban	101-27-9
64	Benalaxyl	71626-11-4
65	Benazolin-ethyl	25059-80-7
66	Bendiocarb	22781-23-3
67	Benfluralin	1861-40-1
68	Benfuresate	68505-69-1
69	Benodanil	15310-01-7
70	Bentazone	25057-89-0
71	Bentazone methyl derivative	N/A
72	Benthiocarb	28249-77-6
73	Benzo(a)pyrene	50-32-8
74	Benzophenone	119-61-9
75	Benzoylprop ethyl	22212-55-1
76	b-Estradiol	50-28-2
77	BHC alpha isomer	319-84-6
78	BHC beta isomer	319-85-7

No.	Compound name	CAS #
79	BHC delta isomer	319-86-8
80	Bifenox	42576-02-3
81	Bifenthrin	82657-04-3
82	Binapacryl	485-31-4
83	Bioallethrin	584-79-2
84	Bioallethrin S-cyclopentenyl i	28434-00-6
85	Bioresmethrin	28434-01-7
86	Biphenyl	92-52-4
87	Bis(2-ethylhexyl)phthalate	17-81-7
88	Bisphenol A	80-05-7
89	Bitertanol I	55179-31-2
90	Bitertanol II	55179-31-2
91	Bromacil	314-40-9
92	Bromobutide	74712-19-9
93	Bromocyclen	1715-40-8
94	Bromophos	2104-96-3
95	Bromophos-ethyl	4824-78-6
96	Bromopropylate	18181-80-1
97	Bromoxynil	1689-84-5
98	Bromoxynil octanoic acid ester	1689-99-2
99	Buprofezin	69327-76-0
100	Butachlor	23184-66-9
101	Butamifos	36335-67-8
102	Butoxycarboxim	34681-23-7
103	Butralin	33629-47-9
104	Butyl benzyl phthalate	85-68-7
105	Butylate	2008-41-5
106	Butylated hydroxyanisole	25013-16-5
107	Captafol	2425-06-1
108	Captan	133-06-2
109	Carbaryl	63-25-2
110	Carbetamide	16118-49-3
111	Carbofuran	1563-66-2
112	Carbofuran-3-keto	N/A
113	Carbophenothion	786-19-6
114	Carbosulfan	55285-14-8
115	Carboxin	5234-68-4
116	Chinomethionat	02439-01-2
117	Chloramben methyl ester	7286-84-2
118	Chloranocryl	2164-09-2
119	Chlorbenside	103-17-3
120	Chlorbromuron	13360-45-7
121	Chlorbufam	1967-16-4
122	Chlordecone	143-50-0
123	Chlordimeform	6164-98-3
124	Chlorfenethol	80-06-8
125	Chlorfenprop-methyl	14437-17-3
126	Chlorfenson	80-33-1
127	Chlorfenvinphos	470-90-6

No.	Compound name	CAS #
128	Chlorflurecol-methyl ester	2536-31-4
129	Chlormefos	24934-91-6
130	Chlornitrofen	1836-77-7
131	Chlorobenzilate	510-15-6
132	Chloroneb	2675-77-6
133	Chloropropylate	5836-10-2
134	Chlorothalonil	1897-45-6
135	Chlorotoluron	15545-48-9
136	Chlorpropham	101-21-3
137	Chlorpyrifos	2921-88-2
138	Chlorpyrifos Methyl	5598-13-0
139	Chlorthal-dimethyl	1861-32-1
140	Chlorthiamid	1918-13-4
141	Chlorthion	500-28-7
142	Chlorthiophos	60238-56-4
143	Chlorthiophos sulfone	N/A
144	Chlorthiophos sulfoxide	N/A
145	Chlozolinate	84332-86-5
146	cis-Chlordane	5103-71-9
147	Clomazone	81777-89-1
148	Coumaphos	56-72-4
149	Crimidine	535-89-7
150	Crotoxyphos	7700-17-6
151	Crufomate	299-86-5
152	Cyanazine	21725-46-2
153	Cyanofenphos	13067-93-1
154	Cyanophos	2636-26-2
155	Cycloate	1134-23-2
156	Cycluron	2163-69-1
157	Cyfluthrin I	68359-37-5
158	Cyfluthrin II	68359-37-5
159	Cyfluthrin III	68359-37-5
160	Cyfluthrin IV	68359-37-5
161	Cyhalothrin I (lambda)	68085-85-8
162	Cymoxanil	57966-95-7
163	Cypermethrin I	52315-07-8
164	Cypermethrin II	52315-07-8
165	Cypermethrin III	52315-07-8
166	Cypermethrin IV	52315-07-8
167	Cyprazine	22936-86-3
168	Cyprofuram	69581-33-5
169	Cyromazine	6215-27-8
170	d-(cis-trans)-Phenothrin-I	26002-80-2
171	d-(cis-trans)-Phenothrin-II	26002-80-2
172	Dazomet	533-74-4
173	Decachlorobiphenyl	2051-24-3
174	Deltamethrin	52918-63-5
175	Demephion	8065-62-1
176	Demeton-S	126-75-0

No.	Compound name	CAS #
177	Demeton-S-methylsulfon	17040-19-6
178	Desbromo-bromobutide	N/A
179	Desmedipham	13684-56-5
180	Desmetryn	1014-69-3
181	Dialifos	10311-84-9
182	Di-allate I	2303-16-4
183	Di-allate II	2303-16-4
184	Diamyl phthalate	131-18-0
185	Diazinon	333-41-5
186	Dibrom (naled)	300-76-5
187	Dicamba	1918-00-9
188	Dicamba methyl ester	6597-78-0
189	Dicapthon	2463-84-5
190	Dichlofenthion	97-17-6
191	Dichlofluanid	1085-98-9
192	Dichlone	117-80-6
193	Dichlormid	37764-25-3
194	Dichlorophen	97-23-4
195	Dichlorprop	120-36-5
196	Dichlorprop methyl ester	57153-17-0
197	Dichlorvos	62-73-7
198	Diclobutrazol	75736-33-3
199	Diclofop methyl	51338-27-3
200	Dicloran	99-30-9
201	Dicrotophos	141-66-2
202	Dicyclohexyl phthalate	84-61-7
203	Dicyclopentadiene	77-73-6
204	Dieldrin	60-57-1
205	Diethatyl ethyl	38727-55-8
206	Diethofencarb	87130-20-9
207	Diethyl dithiobis(thionoformat)	502-55-6
208	Diethyl phthalate	84-66-2
209	Diethylene glycol	111-46-6
210	Diethylstilbestrol	56-53-1
211	Difenoconazol I	119446-68-3
212	Difenoconazol II	119446-68-3
213	Diflufenican	83164-33-4
214	Dimefox	115-26-4
215	Dimethachlor	50563-36-5
216	Dimethametryn	22936-75-0
217	Dimethipin	55290-64-7
218	Dimethoate	60-51-5
219	Dimethylphthalate	131-11-3
220	Dimethylvinphos(z)	2274-67-1
221	Dimetilan	644-64-4
222	Di-n-butylphthalate	84-74-2
223	Diniconazole	83657-24-3
224	Dinitramine	29091-05-2
225	Dinobuton	973-21-7

No.	Compound name	CAS #
226	Dinocap I	39300-45-3
227	Dinocap II	39300-45-3
228	Dinocap III	39300-45-3
229	Dinocap IV	39300-45-3
230	Dinoseb	88-85-7
231	Dinoseb acetate	2813-95-8
232	Dinoseb methyl ether	6099-79-2
233	Dinoterb	1420-07-1
234	Dinoterb acetate	3204-27-1
235	Di-n-propyl phthalate	131-16-8
236	Dioxacarb	6988-21-2
237	Dioxathion	78-34-2
238	Dioxydemeton-S-methyl	17040-19-6
239	Diphacinone	82-66-6
240	Diphenamid	957-51-7
241	Diphenylamine	122-39-4
242	Dipropetryn	4147-51-7
243	Disulfoton	298-04-4
244	Ditalimfos	5131-24-8
245	Dithiopyr	97886-45-8
246	Diuron	330-54-1
247	Dodemorph I	1593-77-7
248	Dodemorph II	1593-77-7
249	Drazoxolon	5707-69-7
250	Edifenphos	17109-49-8
251	Endosulfan (alpha isomer)	959-98-8
252	Endosulfan (beta isomer)	33213-65-9
253	Endosulfan ether	3369-52-6
254	Endosulfan lactone	3868-61-9
255	Endosulfan sulfate	1031-07-8
256	Endrin	72-20-8
257	Endrin aldehyde	7421-93-4
258	Endrin ketone	53494-70-5
259	EPN	2104-64-5
260	Epoxiconazole	106325-08-0
261	EPTC	759-94-4
262	Erbon	136-25-4
263	Esfenvalerate	66230-04-4
264	Esprocarb	85785-20-2
265	Etaconazole	71245-23-3
266	Ethalfluralin	55283-68-6
267	Ethiofencarb	29973-13-5
268	Ethiolate	2941-55-1
269	Ethion	563-12-2
270	Ethofumesate	26225-79-6
271	Ethoprophos	13194-48-4
272	Ethoxyquin	91-53-2
273	Ethylenethiourea	96-45-7
274	Etridiazole	2593-15-9

No.	Compound name	CAS #
275	Etrimfos	38260-54-7
276	Famphur	52-85-7
277	Fenarimol	60168-88-9
278	Fenazaflor	14255-88-0
279	Fenbuconazole	119611-00-6
280	Fenchlorphos	299-84-3
281	Fenfuram	24691-80-3
282	Fenitrothion	122-14-5
283	Fenobucarb	3766-81-2
284	Fenoprop	93-72-1
285	Fenoprop methyl ester	4841-20-7
286	Fenoxycarb	79127-80-3
287	Fenpropathrin	64257-84-7
288	Fenson	80-38-7
289	Fensulfothion	115-90-2
290	Fenthion	55-38-9
291	Fenthion sulfoxide	N/A
292	Fenuron	101-42-8
293	Fenvalerate I	51630-58-1
294	Fenvalerate II	51630-58-1
295	Fepropimorph	67564-91-4
296	Flamprop-isopropyl	52756-22-6
297	Flamprop-methyl	52756-25-9
298	Fluazifop-p-butyl	79241-46-6
299	Flubenzimine	37893-02-0
300	Fluchloralin	33245-39-5
301	Flucythrinate I	70124-77-5
302	Flucythrinate II	70124-77-5
303	Flumetralin	62924-70-3
304	Fluometuron	2164-17-2
305	Fluorodifen	15457-05-3
306	Fluotrimazole	31251-03-3
307	Flurenol-butyl ester	2314-09-2
308	Flurenol-methylester	1216-44-0
309	Fluridone	59756-60-4
310	Flurochloridone I	61213-25-0
311	Flurochloridone II	61213-25-0
312	Fluroxypyr-1-methylheptyl este	81406-37-3
313	Flusilazole	85509-19-9
314	Flutolanil	66332-96-5
315	Flutriafol	76674-21-0
316	Fluvalinate-tau-I	102851-06-9
317	Fluvalinate-tau-II	102851-06-9
318	Folpet	133-07-3
319	Fonofos	944-22-9
320	Formothion	2540-82-1
321	Fuberidazole	3878-19-1
322	Furalaxyl	57646-30-7
323	Furathiocarb	65907-30-4

No.	Compound name	CAS #
324	Furmecyclox	60568-05-0
325	Heptachlor	76-44-8
326	Heptachlor epoxide	1024-57-3
327	Heptachlor exo-epoxide isomer	28044-83-9
328	Heptenophos	23560-59-0
329	Hexabromobenzene	87-82-1
330	Hexachlorobenzene	118-74-1
331	Hexachlorophene	70-30-4
332	Hexaconazole	79983-71-4
333	Hexazinone	51235-04-2
334	Hexestrol	84-16-2
335	Imazalil	35554-44-0
336	Ioxynil	1689-83-4
337	Iprobenfos	26087-47-8
338	Iprodione	36734-19-7
339	Isazophos	42509-80-8
340	Isobenzan	297-78-9
341	Isobornyl thiocyanoacetate	115-31-1
342	Isocarbamide	30979-48-7
343	Isodrin	465-73-6
344	Isofenphos	25311-71-1
345	Isomethiozin	57052-04-7
346	Isoprocarb	2631-40-5
347	Isopropalin	33820-53-0
348	Isoprothiolane	50512-35-1
349	Isoproturon	34123-59-6
350	Isoxaben	82558-50-7
351	Isoxathion	18854-01-8
352	Jodfenphos	18181-70-9
353	Kinoprene	43588-37-4
354	Lenacil	2164-08-1
355	Leptophos	21609-90-5
356	Leptophos oxon	25006-32-0
357	Lindane	58-89-9
358	Linuron	330-55-2
359	Malathion	121-75-5
360	Malathion-o-analog	1634-78-2
361	MCPA methyl ester	2436-73-9
362	MCPB methyl ester	57153-18-1
363	m-Cresol	108-39-4
364	Mecarbam	2595-54-2
365	Mecoprop methyl ester	23844-56-6
366	Mefenacet	73250-68-7
367	Mefluidide	53780-34-0
368	Menazon	78-57-9
369	Mephosfolan	950-10-7
370	Mepronil	55814-41-0
371	Metalaxyl	57837-19-1
372	Metamitron	41394-05-2

No.	Compound name	CAS #
373	Metasystox thiol	919-86-8
374	Metazachlor	67129-08-2
375	Methacrifos	62610-77-9
376	Methamidophos	10265-92-6
377	Methfuroxam	2873-17-8
378	Methidathion	950-37-8
379	Methiocarb	2032-65-7
380	Methiocarb sulfone	2179-25-1
381	Methiocarb sulfoxide	2635-10-1
382	Methomyl	16752-77-5
383	Methoprene I	40596-69-8
384	Methoprene II	40596-69-8
385	Methoprotryne	841-06-5
386	Methoxychlor	72-43-5
387	Methyl paraoxon	950-35-6
388	Methyl parathion	298-00-0
389	Methyl-1-naphthalene acetate	2876-78-0
390	Methyldymron	42609-73-4
391	Metobromuron	3060-89-7
392	Metolachlor	51218-45-2
393	Metolcarb	1129-41-5
394	Metribuzin	21087-64-9
395	Mevinphos	7786-34-7
396	Mirex	2385-85-5
397	Molinate	2212-67-1
398	Monalide	7287-36-7
399	Monocrotophos	6923-22-4
400	Monolinuron	1746-81-2
401	Myclobutanil	88671-89-0
402	N,N-Diethyl-m-toluamide	134-62-3
403	N-1-Naphthylacetamide	N/A
404	Naphthalic anhydride	81-84-5
405	Napropamide	15299-99-7
406	Nicotine	54-11-5
407	Nitralin	4726-14-1
408	Nitrapyrin	1929-82-4
409	Nitrofen	1836-75-5
410	Nitrothal-isopropyl	10552-74-6
411	N-Methyl-N-1-naphthyl acetamid	N/A
412	Norflurazon	27314-13-2
413	Nuarimol	63284-71-9
414	o,p'-DDD	53-19-0
415	o,p'-DDE	3424-82-6
416	o,p'-DDT	789-02-6
417	Octachlorostyrene	29082-74-4
418	o-Dichlorobenzene	95-50-1
419	Omethoate	1113-02-6
420	o-Phenylphenol	90-43-7
421	Oryzalin	19044-88-3

No.	Compound name	CAS #
422	Oxabetrinil	74782-23-3
423	Oxadiazon	19666-30-9
424	Oxadixyl	77732-09-3
425	Oxamyl	23135-22-0
426	Oxycarboxin	5259-88-1
427	Oxychlordane	27304-13-8
428	Oxydemeton-methyl	301-12-2
429	Oxyfluorfen	42874-03-3
430	p,p'-DDD	72-54-8
431	p,p'-DDE	72-55-9
432	p,p'-DDT	50-29-3
433	Paclobutrazol	76738-62-0
434	Paraoxon	311-45-5
435	Parathion	56-38-2
436	p-Dichlorobenzene	106-46-7
437	Pebulate	1114-71-2
438	Penconazole	66246-88-6
439	Pendimethalin	40487-42-1
440	Pentachloroaniline	527-20-8
441	Pentachloroanisole	1825-21-4
442	Pentachlorobenzene	608-93-5
443	Pentachloronitrobenzene	82-68-8
444	Pentachlorophenol	87-86-5
445	Pentanochlor	2307-68-8
446	Permethrin I	52645-53-1
447	Permethrin II	52645-53-1
448	Perthane	72-56-0
449	Phenamiphos	22224-92-6
450	Phenkapton	2275-14-1
451	Phenoxyacetic acid	122-59-8
452	Phenthoate	2597-03-7
453	Phorate	298-02-2
454	Phosalone	2310-17-0
455	Phosfolan	947-02-4
456	Phosmet	732-11-6
457	Phosphamidon I	13171-21-6
458	Phosphamidon II	13171-21-6
459	Phthalide	27355-22-2
460	Picloram methyl ester	14143-55-6
461	Pindone	83-26-1
462	Piperalin	3478-94-2
463	Piperonyl butoxide	51-03-6
464	Piperophos	24151-93-7
465	Pirimicarb	23103-98-2
466	Pirimiphos-ethyl	23505-41-1
467	Pirimiphos-methyl	29232-93-7
468	Plifenat	21757-82-4
469	p-Nitrotoluene	99-99-0
470	Pretilachlor	51218-49-6

No.	Compound name	CAS #
471	Probenazole	27605-76-1
472	Prochloraz	67747-09-5
473	Procymidone	32809-16-8
474	Profenofos	41198-08-7
475	Profluralin	26399-36-0
476	Promecarb	2631-37-0
477	Prometon	1610-18-0
478	Prometryn	7287-19-6
479	Propachlor	1918-16-7
480	Propamocarb	24579-73-5
481	Propanil	709-98-8
482	Propargite	2312-35-8
483	Propazine	139-40-2
484	Propetamphos	31218-83-4
485	Propham	122-42-9
486	Propiconazole-I	60207-90-1
487	Propiconazole-II	60207-90-1
488	Propoxur	114-26-1
489	Propyzamide	23950-58-5
490	Prothiofos	34643-46-4
491	Prothoate	2275-18-5
492	Pyracarbolid	24691-76-7
493	Pyrazon	1698-60-8
494	Pyrazophos	13457-18-6
495	Pyrazoxyfen	71561-11-0
496	Pyributicarb	88678-67-5
497	Pyridaben	96489-71-3
498	Pyridaphenthion	119-12-0
499	Pyridate	55512-33-9
500	Pyridinitril	1086-02-8
501	Pyrifenox I	88283-41-4
502	Pyrifenox II	88283-41-4
503	Pyrimethanil	53112-28-0
504	Pyroquilon	57369-32-1
505	Quinalphos	13593-03-8
506	Quinoclamine	2797-51-5
507	Quizalofop-ethyl	76578-14-8
508	Resmethrin	10453-86-8
509	S,S,S-Tributylphosphorotrithio	78-48-8
510	Sebuthylazine	7286-69-3
511	Secbumeton	26259-45-0
512	Simazine	122-34-9
513	Simetryn	1014-70-6
514	Sulfotep	3689-24-5
515	Sulfur (S8)	10544-50-0
516	Sulprofos	35400-43-2
517	Swep	1918-18-9
518	Tamoxifen	10540-29-1
519	TCMTB	21564-17-0

No.	Compound name	CAS #
520	Tebuconazole	107534-96-3
521	Tebutam	35256-85-0
522	Tecnazene	117-18-0
523	Temephos	3383-96-8
524	Terbacil	5902-51-2
525	Terbucarb	001918-11-2
526	Terbufos	13071-79-9
527	Terbumeton	33693-04-8
528	Terbuthylazine	5915-41-3
529	Terbutryne	886-50-0
530	Tetrachlorvinphos	961-11-5
531	Tetradifon	116-29-0
532	Tetraethylpyrophosphate (TEPP)	107-49-3
533	Tetramethrin I	7696-12-0
534	Tetramethrin II	7696-12-0
535	Tetrapropyl thiodiphosphate	3244-90-4
536	Tetrasul	2227-13-6
537	Thenylchlor	96491-05-3
538	Thiabendazole	148-79-8
539	Thiofanox	39196-18-4
540	Thiometon	640-15-3
541	Thionazin	297-97-2
542	Tiocarbazil I	36756-79-3
543	Tiocarbazil II	36756-79-3
544	Tolclofos-methyl	57018-04-9
545	Tolylfluanid	731-27-1
546	trans-Chlordane	5103-74-2
547	Triadimefon	43121-43-3
548	Triadimenol	55219-65-3
549	Tri-allate	2303-17-5
550	Triamiphos	1031-47-6
551	Triazophos	24017-47-8
552	Tributyl phosphate	126-73-8
553	Tributyl phosphorotrithioite	150-50-5
554	Trichlorfon	52-68-6
555	Trichloronate	327-98-0
556	Triclopyr methyl ester	N/A
557	Tricyclazole	41814-78-2
558	Tridiphane	58138-08-2
559	Trietazine	1912-26-1
560	Triflumizole	68694-11-1
561	Trifluralin	1582-09-8
562	Tryclopyrbutoxyethyl	64470-88-8
563	Tycor (SMY 1500)	64529-56-2
564	Uniconizole-P	83657-17-4
565	Vamidothion	2265-23-2
566	Vernolate	1929-77-7
567	Vinclozolin	50471-44-8

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