

Inductively Coupled Plasma Mass Spectrometry

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BACKGROUND

Inductively coupled plasma mass spectrometry (ICPMS) is a powerful technique allowing the multielemental ultratrace analysis of a wide variety of samples. Several people (among users, manufacturers, etc.) consider it to be a routine technique. In fact, the sales of ICPMS instruments are increasing by approximately 10% per year (A1). Therefore, it is not surprising that, since the last fundamental review was published in *Analytical Chemistry* (A2), the number of its applications has continued to increase. What is amazing is that the concurrent number of fundamental studies further declined, despite the fact that several important shortcomings remain to be resolved. Until they are, the technique will continue to lack the robustness required for what this author would call a genuine routine technique. The purpose of this paper is to critically review significant developments in the ICPMS field during the period from October 2003 to October 2005 (exclusively). This review is not meant to be comprehensive, as it must be limited to a maximum of about 200 references. Nonetheless, it includes several references to relevant books and review papers that provide a more comprehensive coverage.

A search of *Chemical Abstracts* for “inductively coupled plasma mass spectrometry” papers published in 2003–2005 gave some 1434 listings. Since the majority were applications while this review is mainly focused on the fundamentals, and that several important papers relevant to ICPMS may have been missed if they did not contain these key words, selected journals, to which the university library of the author has subscriptions, were systematically perused instead. These include the following: *Analyst*, *Analytical Chemistry*, *Analytical Chimica Acta*, *Canadian Journal of Analytical Sciences and Spectroscopy*, *CRC Critical Reviews in Analytical*

Chemistry, *Analytical and Bioanalytical Chemistry*, *International Journal of Mass Spectrometry*, *Journal of Analytical Atomic Spectrometry*, *Journal of the American Society for Mass Spectrometry*, *Microchemical Journal*, *Mikrochimica Acta*, *Rapid Communications in Mass Spectrometry*, *Spectrochimica Acta, Part B*, *Talanta*, and *Trends in Analytical Chemistry*. (Again, the journal that consistently contained the greatest number of papers on ICPMS was the *Journal of Analytical Atomic Spectrometry*.) Nonetheless, this perusal alone led to over 535 references (including numerous applications)!

However, scrutiny of these references revealed a recurrent problem: the originality of many papers is marginal at best. This is partly due to a growing tendency by authors to review only the recent literature. As a result, numerous papers do not represent a significant advance over what was published some 20 years ago, when ICPMS had just been commercially introduced. Referees should therefore pay particular attention to the cited literature when reviewing manuscripts. The large number of journals available does not help alleviate this problem. Indeed, on several occasions, this author recommended rejection of some manuscript, to later receive the same manuscript from a different journal. This would have been acceptable if the manuscript had been modified to address the concerns raised previously. However, the authors demonstrated a lack of professionalism by submitting an identical, unmodified one. This author has had some manuscripts rejected, which were modified to address the reviewers' concerns before being submitted to a different journal, where they were eventually accepted (often after more revisions). That is the purpose of the refereeing process: to ensure the quality and significance of published papers. The many published papers of marginal significance therefore indicate a large variation in the reviewing process from journal to journal and even within a given journal, which is highly dependent on the referees who are selected. (Note that this observation also applies to fields other than ICPMS.) Journal editors should therefore carefully select reviewers. For the process to be most fruitful, not only should the referees be knowledgeable in the area but they should also be critical.

Conferences. Of the numerous conferences being held, only one remains that is mostly on ICPMS: the Winter Conference on Plasma Spectrochemistry. It is held in the United States and Asia on even years and in Europe on odd years. For example, it was in Tucson, AZ, in January 2006 and will be in Bangkok, Thailand, from November 27 to December 3, 2006, in Taormina, Italy, February 18 to 23, 2007, and at the Pechanga Resort & Casino in Temecula, CA, January 6–12, 2008. There used to be the International Conference on Plasma Source Mass Spectrometry, which was held in September on even years at the World Heritage Durham Castle in Durham, England. However, Grenville Holland, the main organizer of this event, retired from academia

Table 1. Books Related to ICPMS

title	authors/editors	publisher	year	reviewer	ref
<i>Hyphenated Techniques in Speciation Analysis</i>	J. Szpunar, R. Łobiński, Eds.	Royal Society of Chemistry	2004	J. Pawliszyn	A3
<i>Methods for Environmental Trace Analysis</i>	J. R. Dean	John Wiley and Sons	2003	S. Lacorte	A4
<i>Acceleration and Automation of Solid Sample Treatment; Techniques and Instrumentation in Analytical Chemistry 24</i>	M. D. Luque De Castro, J. L. Luque García	Elsevier	2002	J. R. Dean	A5
<i>Handbook of Elemental Speciation: Techniques and Methodology</i>	R. Cornelis, J. Caruso, H. Crews, K. Heumann, Eds	John Wiley and Sons	2003	F. C. Adams, P. B. Stockwell, D. J. Butcher	A7–A9
<i>Sample Preparation for Trace Element Analysis; Comprehensive Analytical Chemistry Series XLI</i>	Z. Mester, R. Sturgeon, Eds.	Elsevier	2003	C. Bendicho, D. N. Rutledge	A10, A11
<i>Atomic Spectroscopy in Elemental Analysis; Analytical Chemistry Series</i>	M. Cullen, Ed.	Blackwell Publishing	2004	E. H. Hansen	A12
<i>A Practical Guide to ICP-MS</i>	R. Thomas	Marcel Dekker Inc.	2004	D. C. Grégoire	A13
<i>Applications of Inorganic Mass Spectrometry</i>	J. R. de Laeter	John Wiley & Sons, Inc.	2001	S. K. Aggarwal	A14

in 2004. So far, nobody has indicated any intention of picking up the ball that Grenville had rolling for nine biennial conferences, which were all successful. Then again, with the Winter Conference being held in Europe on odd years, is there really a need to have another mostly ICPMS conference in Europe on even years?

In any case, people with wider interests (such as molecular spectroscopy) may prefer to attend the annual meeting of the Federation of Analytical Chemistry and Spectroscopy Societies (FACSS) or the International Conference on Analytical Sciences and Spectroscopy (ICASS) that is held annually in Canada. The latter has the same high quality but is smaller in size than FACSS so that there are less choices to make as to which talk to attend (for this reason, this author personally prefers ICASS). In any case, FACSS 2006 will be held September 24–28, 2006, at Disney's Contemporary Resort, Lake Buena Vista, FL (see <http://facss.org>) whereas the 52nd ICASS will be held in Kelowna, in the beautiful Okanagan Valley of British Columbia, June 18–22, 2006 (see <http://www.icass2006.ca>). Information on other conferences involving ICPMS can be found in various journals. The digitized *ICP Information Newsletter*, edited by Ramon M. Barnes (who is also the organizer of the Winter Conference on Plasma Spectrochemistry in the United States), publishes reports on symposia and plasma-related abstracts of papers presented at numerous conferences worldwide in addition to a calendar of plasma-related events.

Books and Reviews. Table 1 lists detailed reviews written by experts on books that either contain at least one chapter on ICPMS or are very relevant to ICPMS practitioners. Review articles on specific topics are referenced in the relevant following sections. Given the large number of published ICPMS papers, numerous general review articles were also published. For instance, several reviews on atomic mass spectrometry (A15–A17) and atomic spectroscopy (A18) included significant developments in instrumentation, methodology, and understanding of the fundamentals of ICPMS. Of course, ICPMS continued to be prominently used in numerous applications, such as for the determination of the following: long-lived radionuclides in radioactive waste solutions, water samples, soils, sediments, and body fluids (A19); major to ultratrace elements in biological systems

(A20); elements in industrial products including metals, chemicals (organic, inorganic, and petroleum products), and advanced materials (polymers, composites, glasses, ceramics, catalysts, etc.) (A21, A22); elements, including platinum group elements and Au, and their speciation in environmental samples (air, water, soil, plants, geological materials, etc.) (A23–A27); elements and their speciation in clinical and biological materials, food, and beverages (A28, A29), including wine (A30); elements in geochemical and cosmochemical materials (A31)

SAMPLE PREPARATION

A crossing between the conventional oxygen flask combustion and modern microwave digestion was implemented for the digestion of organic samples (B1). With this new approach, 50–250 mg of sample is weighed directly on paper, in which it is then wrapped and placed in a quartz holder. An igniter (50 μ L of 6 M NH_4NO_3) is added to the paper and the holder is placed in a regular high-pressure quartz vessel already containing 6 mL of concentrated nitric acid, which is used as absorbing solution. The closed vessels are then pressurized with 5–15 bar O_2 for 2 min while the microwave oven is operated. The resulting solution is then diluted with water and analyzed. For bovine liver, which has a relatively high carbon content, the residual carbon was $\sim 1.3\%$, which could be reduced to 0.4% if the absorbing solution was refluxed 8 min (B1). Although this approach is in its infancy, it is clearly promising. Further studies are warranted to identify the exact mechanism of combustion and to investigate the effect of various parameters (such as holder design, type of absorbing solution, reflux time, etc.).

Another way of avoiding the use of large volumes of strong acids as well as the safety hazards associated with the use of aqua regia and HF was described (B2). It enabled an environmentally friendly digestion of soils and sediments for the determination of the total concentrations of Pb, Cd, and Sb (B2). The procedure involved drying the sample mixed with magnesium nitrate (10%, v/v) on a hot plate, followed by ignition in a muffle furnace using a stepwise temperature ramp, and extraction of the residue in 10 mL of HNO_3 (1:1) in a horizontal shaker (B2). Using magnesium nitrate as an ashing aid prevented loss of analytes by volatilization

or adsorption onto the walls of the reaction vessel and produced a readily soluble analyte residue (B2). However, unless many samples can be processed in parallel, the sample throughput may be lower than by the modified oxygen flask method described above, since the procedure takes ~9 h.

An alternative to conventional acid digestion and ashing methods is to use advanced oxidation processes (B3). These include UV irradiation, ozone generation, or ultrasonication. They generate highly potent chemical oxidants in situ, such as hydroxyl radicals and hydrogen peroxide in the case of aqueous solutions (B4), thereby eliminating potential sources of contamination, eliminating reagent consumption, simplifying sample preparation, and reducing the risk that a volatile analyte may be lost since all these processes are carried out at room temperature (B3). As a result, sample preparation is less time-consuming and minimal skill is required of the operator (B3). Numerous examples of applications were described (B3). The use of ultrasonication to assist leaching of solid sample is often a fast, inexpensive, and efficient alternative to conventional, supercritical fluid, and microwave-assisted leaching, as was demonstrated by a review of applications to both organic and inorganic analytes in a wide variety of samples (B4). Whether applied discontinuously or in a continuous flow system, it results in high extraction efficiencies in a short time, with reduced solvent consumption (B4). Ultrasonication can similarly be applied to significantly enhance the kinetics and selectivity of chemical reactions (B4). For example, as will be seen in Table 5, the enzymatic hydrolysis of biological samples for the extraction of Se species, which typically takes 24 h (C77), was reduced to 2 min with sonochemistry (C76).

An article coauthored by Hansen, one of the co-inventors of flow injection (FI), reviewed the extensive use of FI on-line with ICPMS for performing on-line sample pretreatment i.e., matrix separation and analyte preconcentration (B5). Various features of the newer generations of FI, namely, sequential injection (SI) and, more recently, SI with a lab-on-valve (SI-LOV) are also discussed. FI usually employs continuous, unidirectional peristaltic pumping of carrier and reagent streams to implement virtually any type of operation on-line to ICPMS. On the other hand, SI involves a programmable, bidirectional discontinuous flow where a syringe pump sequentially aspirates exact volumes of sample and reagent, through a multiposition selection valve, into a holding coil where they are stacked one after the other. The content of the coil is then propelled toward the detector, allowing dispersion and partial mixing on the way, which promotes chemical reaction. SI is therefore more economical than FI in terms of reagent consumption and, as a result, generates less waste. The SI-LOV alternative simply involves an integrated microconduit on top of the selection valve, which may be designed to incorporate all the necessary operations for sample treatment, thus acting as a small laboratory (hence called LOV) (B5).

These approaches offer numerous benefits over the corresponding off-line batch methods, including higher sample throughput, reduced sample and reagent consumption (and hence reduced waste production), improved precision, low limits of detection or determination, and automation. In addition, the fact that equilibrium is rarely reached in these systems can improve selectivity through kinetic discrimination (where a concomitant element does not react as fast as the analyte and is therefore discriminated

against) (B5). Solid-phase extraction (SPE) for selective analyte retention, on-wall adsorption/retention of analyte chelate or precipitate, solvent extraction/back extraction and hydride/vapor generation were critically reviewed (B5). The combination of SI-LOV with bead injection was highlighted as a way of performing SPE on a renewable column, where some fresh slurry of column particles is automatically loaded into a column for each sample injection, hence improving reproducibility and eliminating carry-over effects (B5). FI and SI can also be used to perform on-line metal fractionation studies in solid samples much faster and with reduced contamination compared to off-line batch methods (B6). In particular, dynamic flow-through on-line systems allow a continuous monitoring of the kinetics of metal-leaching processes, which, in turn, provide enhanced information about the inherent environmental risks of a soil, for example, that can act as a source or sink of contaminants (B6). Even in situ monitoring of the analyte released by environmental media can be implemented using a flow-through microdialysis system (B6).

In fact, double-focusing (DF) ICPMS was demonstrated to be the best match for on-line fractionation studies where on-line leaching of a minicolumn of sample is done while continuously monitoring major elements along with trace ones (B7). This approach can reveal which minerals dissolve to release specific trace elements as the latter then display a signal versus time profile identical to that of major elements from the mineral. It also allows accounting of variations in the amounts of scavenger phases that could otherwise appear as false highs and lows in mobile elements. Because fresh reagent is continuously pumped through the sample, reprecipitation problems are effectively minimized (B7). Because of the slower scanning rate of high-resolution ICPMS compared to quadrupole instruments, a micronebulizer at 100 $\mu\text{L}/\text{min}$ was required. An internal standard (In) was also added to all leaching reagents to compensate for matrix effects from different reagents, variations in dissolved matrix, and instrument fluctuations. The mass resolution was adjusted to remove spectroscopic interferences without requiring on- or off-line matrix removal, which allowed the direct determination of numerous elements in very complex, unpredictable, and difficult matrixes (B7). It allowed the distinction of many minerals (albeit not pyrolusite from manganite). The continuous monitoring of isotope ratios as elements are released helps to differentiate sources, such as mineralized from unmineralized samples, from significant differences in their $^{206}\text{Pb}/^{204}\text{Pb}$ despite little difference in elemental compositions during leaching (B7).

The on-line leaching approach was also modified to provide a quick method to assess the maximum bioaccessibility of elements from solid food, where artificial saliva, gastric juice, and intestinal juice are sequentially pumped through a minicolumn of food (B8). Indeed, because the sample is continuously exposed to fresh reagent, the dissolution equilibrium is shifted to the right. Not only is the maximum quantity of elements released, but also the process is shortened to some 10 min as opposed to the several hours required by conventional batch methods (B8). Furthermore, the approach can simultaneously provide information of the fractionation of elements in food samples. For example, in a corn bran standard reference material from National Institute of Standards and Technology (NIST), two different peaks were observed for Pb during leaching by artificial gastric juice, whose

isotopic composition, which is simultaneously and continuously monitored by ICPMS, was significantly different at the 95% confidence level. In fact, the Pb composition of the second peak matched that observed during leaching by artificial saliva (B8). Such information cannot be obtained by other existing techniques since, for batch methods, an average Pb isotopic composition would be measured as the two fractions would be mixed together.

Quantitative analysis of refractory powdered materials by laser ablation is often limited by signal fluctuations arising from the inhomogeneous dispersion of analytes and internal standard in sample pellets. The use of sol–gels was proposed to solve this problem. The powdered sample material can easily be incorporated along with an aqueous internal standard in the precursor mixture to the sol–gel. Because sol–gels are intrinsically highly homogeneous, they provided an ideal dispersing medium for internal standards, which could then better correct for variations in the ablation rate of the sample. Although the sample preparation time is longer than for methods without a drying step, highly accurate and precise analyses were achieved because of the high homogeneity of the sol–gel pellets, which can also be used to readily prepare solid calibration standards (B9). Further investigation is warranted to establish how close the boiling point of the sol–gel material should be to that of the sample. Zirconium sol–gels were found to be more resilient to fractionation problems arising from the production of large particles, which can settle on the way to the detector, because they produced a smaller number of large particles than silica-based sol–gels (B9).

SAMPLE INTRODUCTION

Conventional sample introduction into the ICP is still usually done using a pneumatic nebulizer combined to a spray chamber (C1). However, using a spray chamber as a filtration device, to remove large droplets that the plasma cannot fully volatilize, induces noise, memory effects, and results in an aerosol transport efficiency typically less than 5%, with most of the sample going to waste. One way to alleviate this problem is to desolvate the sample aerosol prior to its entry into the plasma. The use of microwave radiation for this purpose was examined experimentally and with a numerical model (C2). This study revealed that the droplets were too small to absorb microwave radiation (at 2.45 GHz) and that the 51–60% improvement in sample introduction efficiency likely arose from the increased temperature of the surroundings; i.e., desolvation occurred through conductive heating of the aerosol (C2).

With the increasing requirement to reduce or eliminate waste, even more so if it is corrosive, toxic, or radioactive, there has been a push toward the development of total consumption sample introduction systems (C1). Typically, a 1–2-kW ICP cannot tolerate more than 20–40 mg/min of liquid aerosol, which corresponds to a liquid delivery rate of 20–40 $\mu\text{L}/\text{min}$. Yet, high-efficiency micronebulizers can deliver sample at a few microliters per minute. It should therefore be possible to operate such nebulizers to achieve 100% sample introduction efficiency. Indeed, when they operate below 20 $\mu\text{L}/\text{min}$ sample, most of the aerosol evaporates either spontaneously or after impact with the wall of the spray chamber, which then no longer needs a drain and can be designed to maximize evaporation (C1). Hence, minichambers with less than 10-mL volume can be used or even incorporated at

the base of the torch, such as the torch-integrated sample introduction system (TISIS) developed by Mermet and Todoli (C1). In addition to achieving total consumption, such systems significantly reduce memory effects and equilibration time and are better suited as interfaces between systems producing transient signals (such as HPLC, FI, etc.) since their low dead volume minimizes dispersion and peak tailing (C1). Because the whole sample is introduced in the plasma, they also allow injection volumes smaller than 1 μL , whereas no signal would be detected for such quantity with a conventional sample introduction system (C1). The TISIS design was adapted for use with ICPMS, where a microflow concentric nebulizer was coupled to a single-pass, low-volume spray chamber that was then directly attached to the ICP torch (C3). With this system, a 10 $\mu\text{g}/\text{L}$ Co, Ce, and Ti solution was washed out within 4 s and a 100- μL injection of a standard solution resulted in a flat-topped peak with a 50-s signal plateau (C3).

Another high-efficiency, low sample consumption, and zero dead volume sample introduction system was developed, which allows sensitive element-specific detection in organic-rich mobile phases, and does not require drainage, cooling, or the addition of oxygen to the ICP (C4). This total consumption system couples a microflow nebulizer to an 8-mL spray chamber without drain. The nebulizer features a 50- μm -i.d. capillary that provides a stable flow rate over the range 0.5–11 $\mu\text{L}/\text{min}$ without the need for a sheath flow (C4). The tip of the capillary is centered in a sapphire orifice, and its position can be optimized to generate a fine aerosol. This high-efficiency system provided essentially 100% analyte transport efficiency when the flow rate was up to 7.5 $\mu\text{L}/\text{min}$. Since the aerosol droplet size distribution influences oxide formation, bigger droplets resulting in more oxide formation, the levels of oxides and doubly charged ions were checked. Over 0.5–11 $\mu\text{L}/\text{min}$, CeO^+/Ce^+ was 0.3–1%. Doubly charged ions increased under 3 $\mu\text{L}/\text{min}$ but $\text{Ba}^{2+}/\text{Ba}^+$ was steady at $\sim 1.5\%$ over 3–11 $\mu\text{L}/\text{min}$ (C4). Although this sample introduction system was developed as an interface between capillary HPLC and ICPMS, it might also be used for continuous nebulization of minute samples (although its resistance to blockage remains to be established) or for micro FI.

A mathematical model combining a stochastic technique with a Monte Carlo method was developed to study droplet desolvation and trajectories within the ICP. It was implemented into a 2D, time-dependent ICP model, with source terms added to the conservation equations of mass, momentum, and energy of the gas phase to model plasma–droplet interactions for two types of droplet collisions, coalescence and grazing, i.e., two different sample uptake rates (C5). The cooling effect resulting from the introduction of an aerosol was also taken into account, as it was not negligible and increased with sample loading, i.e., sample uptake rate. The height above the load coil of complete desolvation that was predicted by the model was in agreement with experimental results for both monodisperse and polydisperse aerosols, except at low power levels (C5). This height increased linearly with aerosol carrier gas flow rate and decreased in inverse proportion to rf power.

Nebulizers. Because the orientation of a micronebulizer can affect its performance, a systematic rotation of the nebulizer should be carried out to identify the orientation of the gas outlet of the

nebulizer with respect to the sample outlet providing maximum sensitivity (C6). Direct injection nebulizers, which replace the torch injector, also provide quantitative sample introduction in the plasma with lower detection limits than achieved with other types of nebulizers. However, they are more expensive than conventional sample introduction systems and those based on micro-nebulizers (C1). Furthermore, they are not as easy to install and operate, are prone to blockage or melting, and the resulting signal is noisier because the droplet size distribution is broader (as no pre-evaporation occurs). They also seem to be more susceptible to nonspectroscopic interferences (or matrix effects) despite the fact that apparently robust conditions (i.e., high plasma power and low carrier gas flow rate) are used (C1), which may be linked to a deterioration in the ICP thermal characteristics induced by having to process larger droplets.

A demountable and hence lower cost, direct-injection, high-efficiency nebulizer (DIHEN) was described, where the solution capillary is adjustable so that a better optimization may be carried out (C7). Although it is operated at similar aerosol carrier gas flow rates, rf power, and sample uptake rate than regular direct-injection nebulizers, its optimum position is 5 mm, instead of 2 mm, below the torch intermediate tube, which decreases the likelihood of it melting (C7). Furthermore, the aerosol produced has a narrower droplet size distribution and lower mean droplet velocities than the regular DIHEN, which resulted in enhanced sensitivity for 16 analytes spanning the mass range (C7). However, this translated into significantly improved detection limit for only two analytes (As, Se), whereas similar (for the majority of analytes) or even degraded (Mg, Mn, Cu) detection limits were reported. On the other hand, although the oxide levels were similar, the relative oxide ion intensities were reduced compared to those with a regular DIHEN, because of the longer residence time resulting from the lower droplet velocities.

A homemade hydraulic high-pressure nebulizer (HHPN), combined with a desolvation system involving heating (to 160 °C) and cooling (to 0 °C) stages, was used as the sample introduction system for ICP-TOFMS, to allow high sample throughput multi-elemental analysis of digests of biological materials by flow injection (C8). Filtering the sample prior to its injection and degassing the carrier (using an ultrasonic bath) were required to stabilize the nebulizing pressure. Indeed, particles in the micrometer range could partially or totally clog the HHPN nozzle, whereas bubbles in the carrier liquid induced pressure drops (C8). Nonetheless, detection limits obtained with this sample introduction system were improved compared to those obtained on a similar ICP-TOFMS instrument by flow injection hydride generation, which furthermore does not allow the determination of non-hydride-forming elements (C8). As expected, detection limits were degraded compared to those obtained by continuous nebulization with a conventional sample introduction system (i.e., with concentric nebulizer and spray chamber) because of the loss of sensitivity incurred by using the FI mode, which however provided freedom from memory effects (C8).

Another study compared five different micronebulizers in combination with either a 50-mL glass cyclonic spray chamber or a 30-mL polypropylene single-pass spray chamber (C9). The PFA-ST micronebulizer from CPI International was found to offer the best same figures of merit (i.e., sensitivity and detection limits),

which were similar to those with the Meinhard high-efficiency nebulizer (HEN) despite the fact that the PFA-ST operates at about a third of the Ar pressure required by the HEN (C9). The fact that the nebulizer design had essentially no effect on analyte recoveries from digests of bovine liver or mussel tissue indicates that the spray chamber was the main source of matrix-induced suppression of the analytes signals across the mass range (C9).

Spray Chambers. The spray chamber design can have an effect on nonspectroscopic interferences (for example, less pronounced effects have been observed with a cyclonic spray chamber than a double-pass spray chamber) (C9). Improved performance was obtained by using a PFA cyclonic spray chamber in tandem with a PEEK Scott-type spray chamber (C10). This arrangement indeed resulted in signal enhancement of 2.5–3 times, lighter elements being enhanced less than heavier ones. The slightly drier aerosol exiting the two spray chambers also translated in better signal precision by a factor of ~3 (C10). The arrangement was also more matrix tolerant than the cyclonic spray chamber alone, where a 50% suppression of analyte signal could be observed in riverine water (C10). Unfortunately, memory effects, which may be expected to worsen given the increased surface that the sample can come into contact with, were not investigated. In any case, the use of numerical computer simulations should become valuable tools for the design of spray chambers (C11). These simulations indeed offer a less costly and time-consuming means of optimizing the design of spray chambers than their empirical development, through trial and error, which does not guarantee a top performance (C11).

Vapor Generation. A Canadian group (C12) pointed out that the vast knowledge about the volatile chelates that most metals can form was grossly underutilized. Indeed, this knowledge can, for example, be used to perform the gas-phase separation of analyte from troublesome matrix (such as a saline matrix), preconcentrate it, and allow its direct introduction into the ICP. This was demonstrated for the total ultratrace determination of Cr in seawater using isotope dilution with gas chromatography (GC) and detection by sector field ICPMS. In the proposed approach, all the Cr was first reduced to Cr(III) using SO₂, which was then derivatized using trifluoroacetylacetone (TFA) to Cr(TFA)₃. The volatile chelate was then sampled by solid-phase microextraction (SPME) from the aqueous phase, while stirring it, and desorbed onto a 0.5-m GC column. The transfer line temperature (between GC and ICPMS) was not critical in terms of sensitivity over 60–270 °C, but peak tailing decreased as the temperature increased up to 220 °C (no further improvement was noted above this temperature). An increase in the initial GC column temperature also resulted in a sharper analyte peak with higher sensitivity up to 180 °C. However, 120 °C had to be used for the analysis to provide enough sampling points across the transient peak. The solventless extraction feature of SPME eliminated the solvent peak that was observed when an extract of the chelate in hexane was injected instead, which allowed the use of the sector field instrument in low-mass resolution where its sensitivity is maximal. For a hexane extract, either medium resolution was required to resolve the ArC⁺ interference arising from overlap with the hexane plug (which decreased precision from the concurrent decrease in sensitivity), or the latter had to be separated from the analyte peak using a longer GC column to

Table 2. Selected Chemical Vaporization Quantitation Methods

analytes	sample matrix	vaporization method	detection method (MS type)	calibration strategy	comments	ref
As, Hg, Sb, Se, Sn	sediments, coals, coal fly ash, and sewage sludges SRMs ground to $\leq 50\text{-}\mu\text{m}$ particle size	sample slurry mixed on-line with 1.0% w/v NaBH_4 in 1.0% w/v NaOH; pumped through reaction coil and phase separator; carriers of 4.15% v/v HCl and 0.5% w/v NaBH_4 provided constant background H_2 load to plasma	Perkin-Elmer Sciex ELAN 6000 (Q); 600- μL FI; home-made gas/liquid separator; membrane drying (lowered blanks, except for Hg)	EC ^a with acid-matched or matrix-matched standards	accurate results by acid-matched EC with slurries in 5% v/v aqua regia +50% v/v HCl for Hg, Se, and Sn (sediments), Se (coals, coal fly ash), Hg (sewage sludge); matrix-matched EC required for As; 16.6% v/v HCl suitable for EC of Hg, Sb, and Sn (sediments)	C15
Cd, Hg, Pb, Se	sediment SRMs	same as C15	same as C15	ID ^b (enriched isotope spikes to initial slurry)	12-h standing time required; higher acid concn than when trapping vapor in ETV-ICPMS but shorter measurement time	C16
^{129}I	sediments	sample combusted in a flow of O_2 in oven at 1000 °C; iodine collected on cooled finger; thermal desorption into ICPMS	Micromass Platform ICP (Q); hexapole collision cell with O_2 -He mixture		CC with O_2 -He used to eliminate $^{129}\text{Xe}^+$ interference on long lived ^{129}I ; detection limit of 0.4 pg/g using preconcentration on cooled finger	C17
$^{200}\text{Hg}^{2+}$, CH_3 , $^{201}\text{Hg}^+$	zooplankton from biological tracer expt in aq system	digested sample (to convert all Hg to inorg Hg) mixed with 2% stannous chloride in 1 M HCl in cold vapor cell	Thermo Finnigan Element 1 (DF) but $R = 300$; LI-2 cold vapor system (Bjoern Klaue)	ID with ^{199}Hg (added prior to sample digestion)	correction for dead time and mass bias using blank and 3 Hg standards; algebraic deconvolution of spectra from different Hg sources	C18
As and Hg species	river water	200 μL injected onto HPLC; effluent merged with 1 M HCl and 0.5% NaBH_4 in 1.0% NaOH for on-line hydride generation	Agilent HP 4500; gradient reversed phase HPLC; homemade gas/liquid separator	MSA ^c	no ArCl^+ interference from removal of Cl through vapor generation; degraded sensitivity from compromise conditions for multielemental speciation but higher sample throughput	C19

^a EC, external calibration. ^b ID, isotope dilution. ^c MSA, method of standard addition.

allow detection in low resolution (C12). With SPME, the 0.5-m GC column only acted as an extension of the transfer line. It provided an analysis time of 2 min (versus 15 min with a 30-m column), which is negligible compared to the time required for sample processing (15 min for reduction, 2 h for derivatization, and 25 min for SPME sampling).

The same group demonstrated that UV irradiation of solutions containing As(III), Bi(III), Sb(III), Se(IV), Te(IV), Pb(IV), Sn(IV), Cd(II), Hg(II), Ni(II), Co(II), Fe(III), Ag(I), Au(III), Rh(III), Pd(II), Pb(II), I(I), and S(VI) generated volatile species of these analytes (C39). The analyte solution was simply placed in a septum-sealed 100-mL glass batch reactor, where UV irradiation was done by inserting a pen lamp in a quartz finger at the center of the reactor, immersed in the analyte solution. Sparging of gaseous products with Ar at 20–100 mL/min into the plasma was done continuously (with a makeup of 1 L/min Ar). In general, a very low signal was observed during the first 10 s of UV irradiation, followed by a rapid signal increase, and then either an exponential signal decrease or a plateau (C13). The signal response either ceased or decreased very slowly when the UV light was turned off. These observations suggest three distinct steps: reduction of ions; formation of volatile compounds; and transfer to the gas phase.

These steps appeared to occur very rapidly for Te, Hg, and I but more slowly for other analytes, resulting in tailing of the signal when the UV light was switched off (C13). The time required for UV irradiation was also found to be dependent on the acid use, which suggests that different molecular species may be formed. However, given the fact that significant signal was observed for a large number of analytes, work is warranted on not only identifying the products but also finding the operating conditions that would maximize the yield and lead to viable analytical applications.

The development and application of chemical vapor generation to elemental and speciation analysis was reviewed (C14). Many of the metals and semimetals of the periodic table can indeed be volatilized (as fluorides, chelates, cold vapors, carbonyls, oxides, hydrides, or alkyls) at room temperature and atmospheric pressure (C14). The discovery of new species and methods for their generation, collection, and detection, which is inevitable, will further enhance the application of this technique to both trace element analysis and organometallic speciation analysis (C14). Examples of such applications are given in Table 2.

Electrothermal Vaporization. Despite the fact that the combination of electrothermal vaporization (ETV) with ICPMS is included among emerging environmental analysis techniques in

a recent review article (A26), it remains mostly ignored by the majority of ICPMS users. In fact, ICPMS instrument manufacturers no longer offer ETV as an optional sample introduction system. The onus is thus on the few ETV-ICPMS practitioners to demonstrate the numerous advantages of this technique so clearly that the demand will grow for them, which will force manufacturers to include them again as options. Table 3 illustrates several of these advantages. Only a small amount of sample is needed, which can be either liquid or solid. No waste is generated. A simple external calibration is often possible, which arises from the vaporization of matrix components prior to the analytes, hence eliminating matrix effects and several sources of spectroscopic interference. The ETV can also serve as a preconcentration medium where the chemical vapor generated through hydride generation, cold vaporization, etc., can be accumulated and later released into the ICP. In the section on spectroscopic interferences, the ETV is also shown to be a low-cost alternative to high-resolution ICPMS since it also allows the temporal separation of analytes with different vaporization temperatures, hence resolving isobaric interferences that the currently available high-resolution instruments cannot resolve.

When ETV is used for direct solid analysis, a drift in sensitivity may be observed over time as a result of solid deposition (on the cones, ion lenses, etc.). Such effect could be compensated in many cases using an argon dimer as internal standard (C30). The effect could also be eliminated by filtering large particles exiting the ETV unit, albeit at the cost of reduced sensitivity (C30).

In an interesting study, the ETV was used to coarsely simulate the vaporization behavior within the ICP (C31). An ETV unit, which was inserted between a laser ablation cell and the ICP, was used to heat the ablated aerosol of single-element metallic samples as well as brass and steel. Except for metals with a high vaporization temperature (such as Mo, Ta, and W), an inflection was observed in the ICPMS ion signal during heating of the furnace. Furthermore, the temperature corresponding to this inflection was correlated to the boiling point of the metal (C31). When brass was ablated, Zn was found to have the same profile as when the single Zn metal was ablated, which suggested that Zn fractionated into a single-element phase during ablation. Indeed, the onset temperature of other elements (Ag, Pb, Al, Sn, Cu) decreased compared to that observed for single-element metals, which indicates that they were alloyed in the Cu phase (C31). In the case of steel, most elements did not follow the profile of the corresponding single-element metals.

Particle size analysis carried out in parallel to ICPMS monitoring revealed a correlation between the change in total particle volume and the melting points of metals (C31). For low-melting metals (Ga, Sn, Pb, Cd, Zn), the small particles were entirely removed and the number of large particles decreased when the ETV was held at 2400 °C. For metals with intermediate melting points (Al, Ag, Au, Cu, Mn, Si, Ni, Co, Ti), no change in particle size distribution resulted, only a decrease in the number of particles generated, whereas the ETV at 2400 °C had no effect on the particle size distribution of high-melting elements. A decrease in ICPMS ion signal was also observed when the ETV was held at 2400 °C instead of at 20 °C, which was not correlated to the total particle volume and suggests that the ETV affected

not only the fraction of larger particles but also the total particle size distribution of low-melting metals (C31). Overall, this study showed that particle vaporization could occur at different heights within the ICP, which depended on their size and sample matrix. The ETV might also be used for the selective removal of different elements, which would make it valuable for on-line removal of interferences in laser ablation (LA)-ICPMS (C31).

Laser Ablation. LA is frequently used for direct solid analysis by ICPMS. Becker reviewed the specific use of LA-ICPMS for the determination of long-lived radionuclides in geological and environmental samples (A19). Another review focused on the environmental and biological applications of LA-ICPMS, which were subdivided into subcategories: food, marine studies (corals and fish otoliths in particular), soils and sediments, archaeology, botanical, tissue, teeth, and others (C32).

Fundamental studies on LA using time-resolved shadowgraph and spectroscopic imaging were also reviewed (C33). It pointed out that the very high photon intensities with femtosecond pulse duration of femtosecond lasers makes them predominantly non-thermal, which may eliminate fractionation and matrix dependence since there is less sample heating, no laser-plasma interaction, and smaller aerosol particle sizes result. This was demonstrated to be true for the analysis of NIST glasses, two monazites, and the CNRS-CRPG zircon standard 91500 (C34). Even though the energy output of the femtosecond laser was less stable than that of the nanosecond laser for which the best analytical conditions were selected, isotopic ratios (Pb/Th, Pb/U, Pb/Pb) were more precise, reproducible, and accurate with the femtosecond than with the nanosecond laser (C34). The results demonstrated that analysis by femtosecond LA-ICPMS was independent of the matrix for these sample types and of the integration time slice (C34). Similarly, the near-IR (775 nm) femtosecond laser ablation of brass had to be done in a low-fluence regime ($<5 \text{ J/cm}^2$) to generate ultrafine aerosols whose total Cu/Zn ratio corresponded to the composition of the bulk material (C35). At fluence regime of $>10 \text{ J/cm}^2$, or using near-IR nanosecond ablation, aerosols departed from the stoichiometry of the bulk material (C35).

Another review focused on developments that can facilitate the optimization and fundamental understanding of LA-ICPMS (C36). Successful use of this technique indeed depends on adequate consideration of the physical properties of the sample, ablation process (i.e., laser operating parameters), composition of the transported material, and atomization and ionization conditions within the ICP (C36). Although the limited availability of standards is an impediment to quantitative analysis by this technique, matrix-dependent nonstoichiometric effects, also called elemental fractionation, when present can preclude analysis without matrix-matched standards. Using lasers with shorter pulse width and wavelength may minimize these effects if the ICP operating conditions are also selected to minimize elemental fractionation from incomplete atomization in the plasma. The latter type of fractionation arises as a result of the wide particle size distribution of the aerosol generated by LA, which may furthermore undergo agglomeration during transport to the plasma (C36). Although matrix dependency remains the Achilles' heel of LA-ICPMS, many applications have been reported where a stoichiometric aerosol is generated, which is then fully atomized in the ICP, so that matrix-independent calibrations could be carried out, even using

Table 3. Selected ETV Quantitation Methods

analytes	sample matrix	sample form; chemical modifier	ICPMS brand (MS type)	calibration strategy	features	ref
I	nonfat milk powder, oyster tissue, apple leaves, sargasso SRMs	4 μ L 25% TMAH and up to 95 μ L sample digest (in TMAH) deposited onto tungsten boat furnace	Seiko II SPQ9000 (Q)	EC	detection limit of 0.09 pg or 0.9 pg/mL (with 95- μ L injections)	C20
Cd, Cu, Fe, Pb, Tl	gasoline	emulsion of gasoline in HNO ₃ , water and Triton X-100 (by sonication); 10 μ L injected into graphite furnace along with 0.1% w/v Pd modifier	PE-Sciex ELAN 6000 (Q) with Perkin-Elmer HGA 600 MS	MSA, matrix matched EC or ID	Pd modifier allowed simultaneous determination of analytes with different volatilities	C21
Ag, As, Cd, Cu, Co, Fe, Mn, Ni, Pb, Sn, Tl	hydrated and anhydrous fuel ethanol, with and without detergent additive	addition of 0.3% v/v HNO ₃ to sample; 20 μ L injected into graphite furnace	PE-Sciex ELAN 6000 (Q) with Perkin-Elmer HGA 600 MS	EC with ethanolic std solns	higher sensitivity in ethanol than in aqueous solutions; ETV eliminates plasma loading with organic solvent	C22
Cd, Cu, Pb, Tl, Se	sediment SRMs	slurry prepared in HNO ₃ , HF and DDW (diluted to 5% HNO ₃ and 1% v/v HF); 10 μ L injected into graphite furnace	PE-Sciex ELAN 6000 (Q) with Perkin-Elmer HGA 600 MS	ID (enriched isotope spikes added to initial slurry)	no modifier required when ID carried out; thermochemical reaction facilitates equilibration	C23
Hg	river sediment, hair, wet freshwater fish	1-mg sample weighed directly into graphite sample boat (sample vapor mixed with ID spike in the furnace)	PE-Sciex ELAN 5000 (Q), SM-30 boat-in-tube graphite furnace	ID using gas flow of ²⁰⁰ Hg transported thru graphite furnace and submitted to same temp program as sample	ID corrects for covaporization matrix effects; single temp program suitable for vastly different samples; additional drying step for wet sample	C24
As, Hg, Se, Sn	sediment SRMs	0.5 mL sample slurry (in aqua regia and HF) treated with 3% (m/v) NaBH ₄ in 1% (m/v) NaOH; hydrides and Hg carried to ETV (previously treated with Ir) by Ar flow during 30 s	PE-Sciex ELAN 6000 (Q); Perkin-Elmer HGA 600 MS and MHS-15 hydride generator	EC	simplified ETV program (no pyrolysis required); Ir permanent modifier allowed efficient trapping of hydrides; might also be applicable to Bi, Cd, Ge, In, Pb, Sb, and Tl	C25
Hg, Pb, Se	sediment SRMs	slurry prepared in aqua regia, HF, and HCl (diluted to 2% aqua regia, 1% v/v HF and 8.5% HCl); 1 mL injected into hydride generator; vapor trapped in ETV	PE-Sciex ELAN 6000 (Q) with Perkin-Elmer HGA 600 MS and MHS-15 hydride generator	ID (enriched isotope spikes added to initial slurry)	no standing time required; Cd could not be determined unlike when vapor directly injected into ICPMS; otherwise similar figures of merit	C16
Be, Co, Pd, Cd	human hair and urine SRMs	10-min 3–5 μ L single drop microextraction of hair digest or 10-fold diluted urine into 0.1 M benzoylacetone; droplet injected in ETV	Agilent 7500a(Q); WF-4C graphite furnace	EC using std solns submitted to micro-extraction too	70-fold analyte enrichment in 10 min by continuous flow microextraction	C26
V, Cr, Mo, Ba, La, Ce, W	human serum	serum diluted 5-fold in 1% HNO ₃ ; 10 μ L injected in furnace; ETV program 1; 10 μ L 6% m/v PTFE ^a modifier then added; ETV program 2	Agilent 7500a(Q); WF-4C graphite furnace	EC	2 temp programs used to achieve in situ matrix removal; allows EC for high sample throughput	C27
U, Th, Pu	oyster tissue, nearshore and open ocean seawaters, estuarine and riverine waters SRMs; urine	preconcentration by co-precipitation of Ca ₃ (PO ₄) ₂ ; dissolution of precipitate in 5% HNO ₃ ; 10 μ L injected onto Ta insert in ETV; 1.4% trifluoromethane in Ar carrier gas	PE-Sciex ELAN DRC II (Q); HGA-600MS; 80-cm long, 6-mm i.d. Teflon transfer line	matrix-matched EC	complete analyte recovery from all matrixes but urine (correction factor then required); Ta and gaseous modifier prevented refractory carbide formation	C28
Ag, As, Cd, Co, Cr, Cu, Mn, Ni, Se, Tl, Zn	fish otolith SRM	sample digested in HNO ₃ ; precipitation of CaF ₃ with HF; 50 μ L of supernatant and 10 μ L of Pd/Rh modifier injected in ETV	PE-Sciex ELAN 5000(Q); HGA-600MS; 65-cm long, 0.6-cm i.d. PTFE transfer line	EC with stds in 1% v/v HNO ₃	no coprecipitation of these analytes; Al, Bi, Pb, and V were lost totally and Fe, Mo, Sb, and Sn partially; precipitating Ca removed spectroscopic interferences on Co and Ni	C29

^a PTFE, poly(tetrafluoroethylene).

solutions through a desolvating systems (C36 and references therein).

The size of the ablated particles can be reduced by applying a second laser pulse within 1 μ s of the first shot (C37). Indeed, double-pulse LA increased the signal intensity 50–100% while the crater volume increased only by 20%. The increased signal intensity was concurrent with a decrease in the number of spikes in the temporal signal, which in turn improved the short-term change in temporal signal by a factor of 2 and the RSD by a factor of 5 (C37). As discussed in the ETV section, inserting such a device between the ablation cell and the ICP could also reduce the particle size distribution, especially for low-melting elements (C31).

Another study demonstrated the feasibility of performing qualitative depth profiling by continuous single-hole drilling of 3- μ m-thick ZrTiN coatings using a homogenized beam from an ArF* 193-nm excimer laser with a 20-cm³ ablation cell (C38). A very small ablation cell (i.e., of 1.5 cm³) was also tried to minimize signal tailing but resulted in memory effects, probably from inertial losses of aerosol on cell walls followed by its delayed mobilization. Both steady-state signals of pure coating and pure substrate and optimum depth resolution were obtained with crater diameters between 20 and 40 μ m (C38). Since almost identical in-depth variation of concentration of coating constituent (Ti) was observed by LA-ICP optical emission spectrometry, a reasonable degree of reproducibility may thus be achieved for depth profiling with LA-ICP spectroscopy. Another study showed that ablation with a 193-nm ArF excimer laser could be used for depth profiling analysis with a spatial resolution sufficient to differentiate between separate layers as thin as ± 1 μ m (C39).

A particle separation device, which allowed the removal of a well-defined fraction of larger particles from the aerosol without changing the volume distribution of the smaller particles, was used in an attempt to determine the smallest particle size of NIST 610 glass SRM that would undergo vaporization and ionization in the ICP (C40). However, after removing the particle size fraction above 150 nm, incomplete vaporization and ionization of the remaining particles was observed in an ELAN 6000 ICPMS system. Single-hole ablations were then used to establish the lower vaporization limit. Indeed, time-dependent measurements of the particle size distribution revealed that a large number of particles of ≥ 1 μ m were generated at the beginning of the ablation, but when a crater depth-to-diameter ratio of ~ 1 was reached, i.e., after 100 laser pulses, the particles became smaller than 90 nm (C40). The integrated ICPMS signal intensities versus the total volume transported were then strongly correlated linearly, with intercepts through zero, indicating that particles smaller than ~ 90 nm were completely ionized within the ICP (C40). The study also showed that the ICP vaporized the more volatile elements from all particle size fractions more efficiently and that stoichiometric LA sampling into transportable particle size fractions below 150 nm (for silicates) is required to reduce elemental fractionation (C40).

Ablation experiments at 266 nm on synthesized lithium tetraborate glass samples containing different amounts of iron oxide contents and 11 trace elements demonstrated that the optical absorption behavior of the sample was a most critical parameter (C41). With increasing optical absorbance, the laser beam had shorter optical penetration depths into the samples, which

translated into higher energy per volume and thus smaller particle sizes in the resulting aerosol (C41). Only a small portion of the ablated volume, corresponding to smaller particles, contributed to the resulting ICPMS signals because of the relatively low transport efficiencies of the ablated material and the incomplete vaporization, atomization, and ionization of the bigger particles in the ICP (C41). As observed in a previous study (C40), elemental fractionation was important at the start of the ablation of samples with low absorption coefficients, when a great number of large particles were generated and was again enhanced when a critical crater depth-to-diameter ratio was exceeded. Hence, only a portion the signal following the prepeak could be used for quantification. Furthermore, the particle size distribution changed so much with ablation time during crater formation that the ablated mass was not proportional to the resulting ICPMS signal. Under these conditions, no straightforward mathematical correction for elemental fractionation could be accomplished, which would prevent matrix-independent quantification. Aerosol filtering experiments also demonstrated that the volatile elements were fractionated into different particle sizes, being enriched in the smaller particles so that filtering of the aerosol would further enhance elemental fractionation instead of reducing it. On the other hand, matching the optical absorption characteristics of the standard and the sample could improve the accuracy of direct solid analysis by LA and warrants further investigations.

In the case of homogeneous materials, an objective optimization procedure was devised to find ablation conditions that minimize elemental fractionation (C42). A multivariate method, principal component analysis (PCA), modified to include *Q* statistics, was indeed successfully used to diagnose how prone an unknown homogeneous material is to elemental fractionation. A series of mass spectra were acquired while changing the laser focus position at constant laser power. PCA comparison of these data to a model built from data obtained under defocus condition (-50 , 0 , and $+50$ μ M), which were believed to induce the lowest degree of fractionation, then clearly revealed the extent of fractionation (C42). Indeed, except at the shallowest and deepest laser focus positions, the *Q*-residuals were observed to be statistically identical at the 95% confidence level when little or no fractionation occurred, but to vary greatly otherwise (C42).

Modeling was done to gain some insight on the nanosecond-pulsed LA of a Cu target in a vacuum (C43). Multiple steps were included: (i) target heating, melting, and vaporization; (ii) expansion of the evaporated material plume; (iii) plasma formation, which generates electrons as well as Cu atoms and ions (Cu⁺ and Cu²⁺); (iv) laser beam absorption by the plasma. These different parts were solved simultaneously as a function of time, during and after the laser pulse, to obtain a global picture of the processes involved. Note that this does not exactly correspond to LA for sample introduction into the plasma, since ablation is then done in a 1-atm background gas. However, preliminary results indicated that most of the modeling results would not be fundamentally different, except that the vapor plume would be considerably shorter; i.e., the biggest difference would be in a slower rate of change of physical properties as a result of a slower expansion than in a vacuum (C43). Another important process that was omitted from the model is the production of particles, despite the fact that they would be the main constituents in the flow to the

ICP. Nonetheless, qualitative agreement, between results of the model and experimental data from the LA-ICP literature, indicates that this relatively simple model already provides a realistic picture of the mechanisms involved in LA (C43). Results of the model included the temperature distribution in the target as well as at its surface, the density, velocity, and temperature distributions in the vapor plume, the effect of the target reflectivity (which is not well known, especially since it can change during the ablation process), and of the laser intensity.

A different model was proposed, which quantitatively predicted the intensity versus time profile resulting from LA in single-shot mode (C44). Because the duration of signal is then orders of magnitude longer than the ablation process, the signal distribution can be taken as depending only on the flow-controlled transport processes. These were modeled for an intermixed ablation chamber, where turbulent flow was favored by placing a nozzle at the inlet of the chamber to favor mixing in its center (C44). The effect of sample position, flush frequency, and number of particles on the shape of the signal for various analytes spanning the mass range and with different ionization potentials was studied. The model showed that, to improve precision, the carrier gas should be as fast as possible inside the chamber while avoiding direct wash out of the chamber. This can be achieved by inserting a small-orifice nozzle at the chamber inlet while placing the chamber exit either at a less exposed position or under a cover (C44). The model may also be used to complete the signal profile from a limited number of data points, which could allow internal standardization using major elements from the sample matrix, based on their incomplete signals prior to detector saturation (C44).

Isotope dilution (ID) is an alternative calibration strategy, which was demonstrated to provide accurate results for various powdered sample types when matrix-matched standards were not available (see ref F15). The powdered sample was simply suspended in a solution of isotopic spike, allowed to dry, and then pressed into a pellet for LA-ID-ICPMS analysis (see ref F15).

The coupling of LA with ICPMS was reported, where a mass spectrograph with the Mattauch–Herzog geometry, i.e., with a flat focal plane, allowed the use of a planar array detector for the simultaneous detection of all m/z values (C45). In combination with a fast washout ablation cell, with a low internal volume of 11 cm³, transient signals of tens of milliseconds in duration could readily be monitored. Because correlated noise could be compensated through calculating the ratio, isotope ratio precision of 0.02% or better could be achieved, which is similar to that obtained using MC instruments (C45).

In fact, like spray chambers, the ablation cells have so far been developed empirically, through trial and error, and are unlikely to provide optimal performance. Computer simulations of the ablation cell and transport tube between the cell and the ICP could be very useful and cost-effective for optimizing their geometrical parameters (C11). In principle, LA-ICPMS can be matrix-independent. Indeed, if there is no preferential evaporation during LA (as femtosecond lasers may provide) and the resulting particles are small enough that they can undergo complete atomization and ionization in the ICP (which is more likely when using robust ICP operating conditions), the only parameter that would be left to optimize is the transport of the aerosol particles within the

ablation cell and through the transport tube to the ICP (C11).

The combination of LA to sector field, double-focusing ICPMS was shown to offer clear advantages for several applications to complex samples (C46). For the direct analysis of tree rings, after a simple drying step, the medium-mass resolution mode was required to resolve ¹³C from ¹²CH. Indeed, even after drying, the residual moisture in the rings induced a loss of ¹³C to ¹³CH, which then biased the Sr results obtained by normalization to ¹³C (C46). A correction could be made using the intensity of ¹²CH multiplied by ¹³C/¹²C concurrently measured in the tree rings. Similarly, for isotope tracing and age determination using U/Pb and Pb/Pb isotopic ratios in U-rich minerals, the laser provided the spatial resolution required to see heterogeneities in single crystals, whereas medium resolution was required to resolve spectroscopic interferences of argides and phosphides on ²³⁵U (C46).

Table 4 gives selected examples of innovative applications of LA-ICPMS. The main advantage of this direct solid analysis technique is that lengthy sample preparation is avoided. This, however, usually comes at the price of reduced precision and degraded detection limits compared to what can be achieved by nebulization of digested samples (C49). Nonetheless, because LA is essentially nondestructive, since it consumes only a minute amount of sample, it is ideally suited for the analysis of forensics materials. The very rapid data acquisition time across the entire periodic table that TOF-ICPMS provides, which allows a more accurate determination of the composition during fast transient signals and hence enables multielemental determination for extremely small samples, was demonstrated to be particularly advantageous for the forensic analysis of microdebris (C53). Although LA-ICPMS is not as yet a reliable, quantitative analytical technique because of the unpredictable nature of ablation, where the amount of ablated material varies with each ablation event and leads to differing amounts of analytes in the plasma, the relative amounts of analytes removed are reproducible (C52). So, a comparison of elemental distribution patterns to indicate comparability of samples was found to be valid (C52).

PCA, which generates a simple two-dimensional map summarizing the main differences (i.e., major variances of samples in a data set), was shown to be a powerful approach for the identification of samples i.e., source matching (C42). The efficiency of this approach at differentiating samples was further enhanced through incorporation of Q -statistics, where a model is generated from the data of one sample and other samples are then compared to it. This approach does not require any subjective judgment since it also generates confidence limits to make the matching procedure totally objective (C42).

When the raw analyte signal is not directly comparable between different samples, such as when attempting to fingerprint diamonds, a standard normal variate transformation can be carried out, where, for every sample, the average and standard deviation of the analyte signals are calculated (C50). Then, the average is subtracted from the signal for every element and divided by the standard deviation. This normalization method therefore sets the mean of all analyte signals to zero and the corresponding standard deviation to one (C50).

Speciation Methods. The use of ICPMS in the life sciences was reviewed (C58). In particular, its ability to discriminate (with isotopic resolution) between analyte (metal, metalloid, or hetero-

Table 4. Selected LA Quantitative Methods

analytes	sample matrix	sample preparation	detection method (MS type)	calibration strategy	feature	ref
7–32 elements	glass and steel SRMs, high-purity Cu	sample mounted on flattened clay (to prevent movement during ablation)	Thermo Finnigan Element 1 (DF) with shielded torch; $R = 300$ or 4000; LA by CETAC LSX-100 with 3-m, 3-mm i.d. transport line to ICP		principal component analysis of rel concn of elements used, with statistical confidence limits added, to quantify the degree of differentiation between samples	C42
Se content and distribution	sulfide minerals		Thermo Finnigan Element 1 (DF); NewWave Research LA systems (LUV 266 and 213); Ar carrier gas	EC with PbS synthesized with 1–10% Se and pressed pellet of Se-doped CuS; S internal std	high resolution required to resolve interferences on Se and S	C46
Pb, Th	tuff (volcanic) rock		VG-Elemental PQ3, NewWave Research LA system (213 nm); Ar carrier gas	EC using NIST glass SRMs with Si internal std	single spot sampling (disregarding the first 15 s of ablation) gave more accurate and precise results than scanning the laser on the sample	C47
Mg, Al, Ti, Mn, Ga, Rb, Sr, Zr, Ba, La, Ce, Hf, Pb, B	glass	surface scratched with 3600 mesh sand paper; washed with MeOH and 0.8 M HNO ₃ , rinsed with DDW and dried	Agilent HP-4500 (Q); CETAC LSX-200 or LSX-500 (preferred for better precision, i.e., <5% RSD)	EC with internal standardization using Si	little fractionation if first 10 s of single-shot LA discarded: 98% of particles are 0.1–0.2 μm	C48
	Stainless steel	disk-shaped sample surface-grinded, rinsed with DDW and acetone and dried with compressed air	PE-Sciex ELAN 6000 (Q); CETAC LSX-100	EC with internal standardization using Fe	less precise and sensitive than wet methods but eliminates sample pretreatment	C49
Al, Hg, Na, Ni, Pb, Sb, Sn, Ti, Zn	diamond	polished, cleaned in concd H ₂ SO ₄ and rinsed with DDW	PE-Sciex ELAN 6100 (Q); GeoLas 193-nm ArF excimer; 16 μg ablated in total from each sample	drift correction using NIST SRM 612 every 2 h; ¹³ C ⁺ not suitable internal std	median of signals from 8 random 30-s LA used for fingerprinting by PLS analysis after std normal variate transformation	C50
multi-element	metallurgical SRMs, modern and Roman coins	3 20-s rubbing of diamond lapping film (DLF) over metal sample with 2 90° rotation; 1 mg sample transferred	PE-sciex ELAN 6100 DRC ^{plus} (Q); CETAC LSX-100 (266 nm)	EC with carbon steel SRMs and ¹³ C as internal std	internal std compensated for disk to disk variability; elevated detection limit for Al, Mn, Cr, and Sb from contamination from DLF polymer backing	C51
elemental distribution patterns	artist paints	prototype cell designed for LA of complete painting; collection of debris onto 25-mm membrane filter; quarter of filter mounted on Perspex disk with superglue for LA-ICPMS	Thermo Analytical PQIII TurboPlus; Fisons High Resolution Nd:YAG 266 nm laser; VG Elemental Nd:YAG laser (1064 nm) for indirect sample analysis	drift in signal response monitored through repeated analysis of glass SRM (in the same way as the sample)	indirect in situ sampling avoids possible damage and contamination from scalpel used to remove paint flake from painting; it provides similar patterns but with lower sensitivity	C52
elemental distribution patterns	steel debris (spherules) as small as 70 μm from crime scenes	sample mounted on Perspex disks using either cyanoacrylate glue or by pressing a sticky Perspex disk on shirt of potential suspect	GBC Optimass 8000 (TOF); VG UV microprobe laser (266 nm)		analysis of single spherule discriminated between debris generated from cutting different safes within 5 min	C53
Cl, Br, I	rocks and sediments SRMs	2 g pulverized sample mixed with enriched spike solution; dried at 75 °C; pressed into pellet	ThermoFinnigan Element 2 (SF); $R = 4000$; LINA Spark-Atomizer system (1064 nm)	ID	laser power density was kept low to prevent fractionation between analyte and isotopic spike	C54

Table 4 (Continued)

analytes	sample matrix	sample preparation	detection method (MS type)	calibration strategy	feature	ref
Ag, Tl, Pb	Pt SRM, Pt nanoclusters	1–5 mg powdered nano-cluster sample placed on high-purity carbon ribbon	PE-Sciex ELAN 6000 (Q); CETAC LSX-200 (266 nm); Aridus (microconcentric nebulizer with membrane desolvation)	on-line ID by passing desolvated aerosol from nebulized spike solution through ablation cell	Cu internal std required to correct for differences in sensitivity between LA ICPMS and ICPMS	C55
U isotope ratios	U isotopic SRMs	20 μ L sample and isotopic SRM solution dropped onto flower leaf; dried 2 h in oven at 75 °C; placed in Peltier-cooled ablation cell	ThermoFinnigan Element (SF); Bioptic laser system (213 nm)	mass bias correction using droplet of U isotopic SRM	accuracy and precision of isotope ratios up to 10 \times better with cooled cell than with regular one	C56
S	petroleum products (premium gasoline, diesel fuel, heating oil); gas oil SRMs	sample mixed with enriched spike solution; placed on Kleenex cosmetic tissue; covered with Mylar foil to prevent evaporation of volatile species	ThermoFinnigan Element 2 (SF); $R = 4000$; LINA-Spark Atomizer system (1064 nm); connection to cyclonic spray chamber with glass wool in its exit port to the ICP	ID with ^{34}S -labeled dibenzothiophene in hexane	C deposition on sampler removed with O_2 in Ar flow between samples; same accuracy and precision as for ID analysis of digests; labeled compound must be synthesized	C57

element)-containing species and analyte-free species is an indisputable advantage of ICPMS (C58, C59). That is why it is increasingly used for the determination of metallobiomolecules (also called metallomes (A20)) in combination with gas chromatography–high-performance liquid chromatography (HPLC), nano-flow HPLC, capillary electrophoresis (CE), or laser ablation of 2D electrophoretic gel (C58, C59). With high-resolution instruments and the development of collision/reaction cells, ICPMS can even be applied to the determination of metal-free biomolecules by allowing the sensitive detection of selected nonmetals (in particular S, P, Cl, Br, and I) (C59). The high sensitivity of ICPMS has increased a trend toward the use of capillary liquid separation techniques because they have the advantages of high separation efficiency, low solvent consumption, and small sample volumes, which is of particular importance in bioanalytical chemistry, where the amount of biological sample available is often limited (C60). This, in turn, has induced the development of improved interface between these capillary techniques and ICPMS. For example, an interface was developed between capillary-LC and collision cell (CC)-ICPMS, which consisted of a modified capillary electrophoresis nebulizer and a homemade 4-mL spray chamber that allowed direct nebulization into the ICP, thereby providing 100% sample transport efficiency, good nebulization stability, and minimal dead volumes (C61).

The spray chamber in fact consisted of a 16-mm-i.d. quartz injector tubing extension that, with the torch injector, corresponded to an internal volume of 4 mL. Because of the 3–4 μ L/min solvent flow rates used, CC-ICPMS could be used with organic gradient conditions without requiring desolvation or background minimization (C61). This should therefore allow new applications, which have so far been mostly prevented because of the incompatibility of the required highly organic mobile phases and the ICPMS detector when the separation is carried out at conventional flow rates.

The speciation of elements in biological samples, in particular that of trace metals binding with proteins and DNA/RNA, which

can be carried out by surfactant-mediated HPLC–ICPMS, was also reviewed (A20). Other reviews focused on the combined use of ICPMS and molecular MS, using either electrospray ionization (ESI) (C62, C63) or matrix-assisted laser desorption/ionization (C2) for speciation analysis in general (C63) or specifically in the life sciences (C62). Indeed, although ICPMS does not provide structural information on unknown molecules, it is invaluable in quickly identifying the fractions of interest that should undergo further characterization by molecular MS. The need for these complementary techniques was similarly stressed in a review of mass spectrometry techniques that have been used for Se speciation in high-Se food supplements, such as high-Se yeast, onions, garlic, and Brazil nuts (C64). Therefore, the development of a user-friendly hybrid instrument performing both elemental and molecular MS would greatly impact speciation analysis (C63), especially in the life sciences, as it would significantly speed up analysis. However, this may require different interfaces between the LC system and ICPMS so that similar chromatographic conditions, in terms of mobile-phase flow rate and composition, may be used for both ESI-MS and ICPMS (C64).

Another article reviewed the use of high-resolution ICPMS (HR-ICPMS) and multicollector ICPMS (MC-ICPMS) for environmental trace metal speciation (C65). Although these instruments are more expensive than quadrupole-based instruments, they have unique features. For instance, HR-ICPMS instruments, when operated in low-mass resolution mode, provide unbeatable detection limits, which are required for many environmental applications. This, combined with the ability of HR-ICPMS to resolve many of the spectroscopic interferences that plague quadrupole ICPMS, explains why it has emerged as an important tool for environmental analysis. On the other hand, high-precision isotopic ratios can be obtained by MC-ICPMS because the simultaneous detection of analyte isotopes eliminates correlated noise. However, the ultimate precision and accuracy of isotopic ratios depends on the absence of chromatographic fractionation effects and drift in mass bias during peak elution, as well as data

processing, in particular the mass bias correction procedure and peak integration of the transient signal resulting from speciation analysis (C65). Speciation analysis of environmental and biological samples by LA-ICPMS, following species separation on electrophoretic gels, was part of a separate review article (C32).

Over the years, the speciation of arsenic, which is toxic in some forms but not in others, has generated so much interest that a review was devoted to recent (i.e., covering the years 2000–2003) developments and applications of various analytical methods (including ICPMS) for As speciation (C66). It includes a review of studies that focused on understanding species stability or instability during sample storage, extraction, or other sample pretreatment, and separation. The stability of As species during sample handling and storage is indeed required in order to obtain reliable results, even more so when assessing possible adverse health effects (C67). Before any speciation study is carried out, the stability of analyte species under the conditions to be used should be assessed. For example, Np(IV) was found to oxidize rapidly to Np(V) even under an Ar atmosphere (C68). To keep the uncertainty of the speciation analysis results under 10%, samples therefore had to be prepared under Ar atmosphere and rapidly injected into the separation system (C68). The effect of any sample pretreatment should similarly be assessed. For example, the effect of various extraction procedures on the concentration of inorganic Hg and methylmercury was studied, where sonication in 5 M HCl induced some conversion of methylmercury into inorganic Hg whereas sonication in 1.2 M HNO₃ did not (C69).

Such preliminary studies are required unless speciated isotope dilution analysis can be carried out to correct for species transformation (C69). This method involves the addition of isotopically enriched spikes of each species to be determined (for example, ¹⁹⁹Hg²⁺ and CH₃²⁰¹Hg⁺ for the determination of inorganic Hg and methylmercury) prior to sample processing. Isotope ratios to a reference isotope (²⁰²Hg) are then measured in the final sample solution, and these ratios are converted into analyte concentrations (after correction for dead time and mass bias). The method can only be used if the analyte possesses enough isotopes that are free of spectroscopic interference (i.e., the number of species plus one). It can also only correct for species transformation if it is not total. For example, treatment of samples with HNO₃/H₂O₂ at room temperature totally converted methylmercury into inorganic Hg, which speciated ID could not correct for (C15). As for all ID methods, a complete equilibration between sample and spike species isotopes is required. Otherwise, biased results may result, as was observed in a study of the effect of different extraction techniques on Hg speciation, where the deconvoluted concentrations were systematically lower than the known concentrations (C69). Selected examples of quantitative speciation analysis methods are listed in Table 5.

Gas Chromatography. A review demonstrated that ICPMS is the most frequently used plasma spectrometry detector for GC (C84). The performance of GC–ICPMS critically depends on the interface between the two techniques, in addition to adequate sample preparation, i.e., that does not alter the speciation of an element. The interface must be designed to maintain volatilized species in the gas phase until they reach the plasma. In general, either a heated transfer line connects the GC outlet directly to

the torch, and optimization of ICPMS operating conditions is then done using Xe in the makeup gas (required for the carrier flow rate to be high enough to penetrate the plasma), or a wet aerosol (from a nebulization/spray chamber system) is merged with the gaseous GC effluent prior to its entry in the plasma (C84). Although the latter facilitates the changeover from aqueous solution analysis to GC detection, it leads to lower sensitivity and degraded detection limits compared to the former approach. Indeed, the absence of an aerosol to desolvate and vaporize leaves more plasma energy available for atomization and ionization of analyte species and also results in lower levels of several interfering polyatomic ions. For even higher sensitivity, a preconcentration step can be used during sample preparation, such as purging and trapping of volatile species (C84). Stir bar sorptive extraction, where a stirring bar coated with a relatively thick layer of PDMS is placed in an aqueous sample for extraction of analyte species during a certain stirring time, is followed by thermal desorption of species in a gas chromatograph. This approach leads to higher extraction efficiencies than SPME as a result of the much larger volume of the PDMS-phase (C84).

Liquid Chromatography. HPLC–ICPMS was identified as “the best available technique for trace element speciation” in a review on As speciation (C67). With the increasing number of life science applications involving very small samples (such as individual cells or human biopsy extracts), capillary HPLC is becoming more popular, along with the need for a high-efficiency, low sample consumption, and zero dead volume interface to ICPMS (C4). As discussed at the beginning of the Sample Introduction section, such an interface was developed, which allowed sensitive element-specific detection in organic-rich mobile phases without requiring drainage, cooling, makeup liquid, or addition of oxygen to the ICP (C4). It was used with a 300-μm-i.d. capillary column, operating at 4 μL/min, for mapping Se peptides in the tryptic digest of a Se-containing protein isolated from selenized yeast. About twice as many peaks could be resolved, independent of the hydrophobic or hydrophilic character of the species, compared to when using HPLC with a 4.6-mm-i.d. column and a conventional interface. The sensitivity of the capillary HPLC–ICPMS system was also close to 100 times more than that achieved with the conventional HPLC–ICPMS.

Pore exclusion/size exclusion chromatography coupled to ICPMS was used to study the uptake of metals (in this case U) by bacteria, a step that is required for the selection of microbes if, for example, they are going to be efficiently used for U removal during the remediation of radioactive waste sites (C85). Using a 0.17% NaCl mobile phase, which was required to prevent cell lyses while minimizing salt deposition, cells (excluded from pores) would elute first, followed by large molecules and, last, small molecules, which were undergoing size exclusion on a column offering a binary distribution of large and small pores. Although the bacterial cells were not expected to generate a metal ion signal, since they resembled 2-μm-diameter wet droplets and should therefore pass through the ICP without or with only partial dissociation, a U signal was clearly detected. However, this signal was noisier than that from an equimolar U solution, and the noise level was well above that expected from either shot noise or counting statistics, which indicates incomplete atomization of the cells (C85).

Table 5. Selected Speciation Methods

analyte species	sample matrix	sample pretreatment	separation method	ICPMS brand (MS type)	calibration strategy	comments	ref
inorganic phosphate anions	food extracts	ultrasonic extraction into DDW; addition of 20% trichloroacetic acid to extract; precipitate discarded; NaOH and then DDW added to supernatant	anion-exchange chromatography; 0.15 mM 1,3,6-naphthalene sodium trisulfonate + 5% methanol eluent	Thermo-Elemental Axiom (R = 3000); using $^{31}\text{P}^+$	MSA	MSA used to compensate for <100% extraction recovery	C70
Cr(III), Cr(VI)	bacterial culture medium	incubation of bacterial culture in the presence of Cr(VI) at 37 °C; samples taken after 0, 2, and 6 h	anion-exchange chromatography; $(\text{NH}_4)_2\text{SO}_4$ 17.5 mM, pH 9.0 eluent	Agilent HP4500 (Q); using $^{53}\text{Cr}^+$	EC using peak area	monitoring of reduction of Cr(VI) by microorganism	C71
Hg^0 , $(\text{CH}_3)_2\text{Hg}$, CH_3Hg^+	air	reduced pressure sampling of air and gaseous tracers thru filter and Carbotrap adsorbent; thermal desorption of species through NaBH_4 ; collection on Tenax TA; cryogenic focusing on Tenax TA adsorbent	thermal desorption into GC; temp programming; He carrier gas;	Agilent 7500a (Q); monitoring ^{198}Hg , ^{199}Hg , ^{200}Hg , ^{202}Hg ,	species-specific ID; gaseous tracers introduced thru permeation tube during sampling	species-specific ID compensated for incomplete collection and desorption of species, and allowed a measure of species transformations	C72
organotin and organo-arsenic species; MeHg	oyster tissue SRM	accelerated solvent extraction (or pressurized fluid extractn) at 100 °C and 1500 psi in 50% acetic acid in MeOH	Sn and Hg by GC with N_2 added to effluent to enhance Sn signal; As by anion exchange LC with O_2 added to ICP; eluent of 1% MeOH, 2.2 mM NH_4HCO_3 /2.5 mM tartaric acid at pH 8.2	Agilent 7500i (Q)	EC (AsB), MSA (other As species, Hg); species-specific ID (Sn)	simultaneous extraction of all species; recovery from 76% (MeHg) to 99% (AsB only); less than 100% recovery compensated by ID or MSA	C73
Hg, MeHg	sea-water	3-min derivatization with NaBPr_4 ; 5-min SPME sampling of headspace	thermal desorption in temp-programmed GC; He carrier gas; homemade GC-ICPMS interface	HP 4500 (Q)	MSA to compensate severe matrix effect from seawater on derivatization	detection limit of 0.2 and 0.4 ng/L for MeHg and Hg, respectively	C74
cisplatin, monoaquacisplatin, diaquacisplatin, carboplatin, oxaliplatin	urine, wastewater	20-fold dilution of urine; filtration of wastewater (0.45 μm)	gradient RP-HPLC with 20 mM ammonium formate/4% v/v MeOH, DDW, and MeOH	PE-Sciex Elan DRC II (Q); PFA nebulizer; cyclonic spray chamber	EC by injecting cisplatin stds in 150 mM Cl^-	separation of all analytes within 6 min	C75
Se species	chicken muscle, liver, kidney	dried sample mixed with Tris-HCl buffer (pH 7.5) and protease XIV, sonicated for 2 min; centrifuged; supernatant passed through 10 kDa cutoff filter; dilution with DDW	cationic exchange HPLC; 4 mM pyridine formate in 3% MeOH (pH 2.8 or 4.7)	Agilent HP-4500; Babington nebulizer, Peltier-cooled Scott double-pass spray chamber	MSA	sample/enzyme mass ratio of 5 provided quantitative recovery in Tris-HCl buffer; activity of enzyme enhanced by sonochemistry; separation within 20 min	C76
Se species	Antarctic krill	lyophilized sample suspended in Tris-HCl buffer (pH 7.5); mixed with Pronase E enzyme; incubated at 37 °C 24 h; centrifuged; supernatant filtered (0.45 μm); SEC filtration (0.45 μm), acidification to 24 mM HCl and refrigeration	RP (C18)-HPLC; 0.1% TFA with 2% MeOH	Agilent 7500s	EC and MSA	sample/enzyme mass ratio of 20 provided quantitative Se extraction	C77
As species	natural waters	filtration (0.45 μm), acidification to 24 mM HCl and refrigeration	anion exchange HPLC; 20 mM $\text{NH}_4\text{H}_2\text{PO}_4$, pH 8.1, spiked with 50 $\mu\text{g/L}$ Rb internal std	VG Plasma-Quad II (Q); concentric nebulizer; water-cooled impact bead spray chamber	EC with internal standardization using Rb	HCl most effective at preventing oxidation of As(III) during storage	C78
Fe(II), Fe(III)	natural waters (lake, tap; mineral, sports)	sample pH adjusted to 6.0	pumped through gallic acid modified nm-sized Al_2O_3 ; Fe(II) unretained; elution of Fe(III) with 1 M HCl	Agilent 7500a (Q); Babington nebulizer	EC	quantitative separation at pH 5.5–6.5 (natural sample pH); except for PO_4^{3-} , unaffected by other cations and anions	C79

Table 5 (Continued)

analyte species	sample matrix	sample pretreatment	separation method	ICPMS brand (MS type)	calibration strategy	comments	ref
Me ₃ Pb ⁺ , MeHg ⁺ , Bu ₃ Sn ⁺ , Bu ₂ Sn ²⁺ , BuSn ³⁺	mussel, tuna fish, dogfish muscle, sediments SRMs; seafood	mild sample digestion; pH adjusted to 5.0; ethylation or propylation of analyte; extraction of derivatized species into hexane; 10-fold preconcn by N ₂ flow through extract	1 μ L injected into splitless GC; 180-cm long, 0.51-mm i.d., 1.59-mm o.d. heated transfer line to ICP	Agilent HP 4500 (Q)	species-specific ID; isotope-labeled spikes added prior to sample dissolution	commercially available isotope-labeled compounds of Hg and Sn; transformation of Hg to MeHg during digestion of sediment	C80
Hg and butyltin compds	natural seawater, snow	sample mixed with isotope-labeled spikes; pH adjusted to 5.0; ethylation or propylation of analyte; extraction of derivatized species into isooctane	3 μ L splitless injection into GC; 0.5-m long, 0.28-mm i.d. heated transfer line to ICP through new interface for dual-sample introduction i.e., mixed wet and dry aerosols	Thermo-Electron \times 7 (Q)	species-specific ID for MeHg, Hg, and TBT; EC for MBT and DBT	simultaneous nebulization of Tl and Sb used for mass bias corrections on Hg and Sn, respectively	C81
seleno-methionine (SeMet), seleno-cysteine (SeCys)	human serum	denaturation of proteins, carboxymethylation of SeCys; destruction of excess alkylating reagent; proteolytic digestion; centrifugation	filtered supernatant injected onto SEC; fractions freeze-dried; lyophilizate dissolved in mobile phase; gradient cHPLC with interface from C12	Agilent 7500c (Q)	⁷⁷ SeMet used for species-specific ID and as internal std for SeCys	collision cell with H ₂ used to eliminate Ar ₂ ⁺ interference; ID allows monitoring of and correction for species transformation	C82
U-binding species	bacterial cell suspensns	cell suspension mixed with pH buffer and U solution	flow field fractionation with 4 mL/min channel flow, 0.4 mL/min cross-flow and 4-min relaxation time; 10 mM NH ₄ Cl/0.005% v/v Triton carrier	PE-Sciex Elan DRC (Q); concentric nebulizer; cyclonic spray chamber		hyperlayer flow FFF separated cells from exopolymers and allowed study of competitive metal binding between bacterial strains	C83

Capillary Electrophoresis. Two different micronebulizers were compared for their use as an interface for CE to ICPMS, in combination with a Cinnabar cyclonic spray chamber (C68). Although the MCN 100 had an efficiency of aerosol formation 1.25–2 times than of the MicroMist, its long-term stability was unsatisfactory (it was prone to blockage problems), so the MicroMist was selected because it offered good long-term signal stability (C68). Because the coupling of CE to ICPMS is not as straightforward as that of HPLC to ICPMS, several interfaces were reviewed, which are based on either nebulizers or on vapor generation (C86). Micronebulizers are most recommended for the former approach, since their uptake rate is more compatible to the CE flow rate, which minimizes unwanted suction effects while enhancing analyte transport efficiency. They should be used in combination with a low-volume spray chamber to minimize band-broadening and avoid long sample washout times. If the analyte can be selectively transformed into a gaseous species through a vapor generation interface, then 100% analyte transport efficiency can be achieved along with a separation from the liquid matrix. This provides maximum flexibility in the selection of the mobile phase and can result in enhanced ionization efficiency in the plasma since its energy is then only needed for atomization and ionization of the analyte (C86).

A low-flow, Mira Mist CE parallel path nebulizer was used in combination with a jacketed cyclonic spray chamber as an interface for either CE–ICPMS or μ HPLC–ICPMS (C87). There are no suction effects with this nebulizer since it is not self-

aspirating. The parallel path design also avoids nebulizer clogging, which keeps its maintenance very simple (C87). In combination with a makeup flow of 15 μ L/min 20% methanol, gradient elution could be carried out in μ HPLC without inducing changes in ICPMS sensitivity. Indeed, since it operated at a nanoliter per minute flow rate, the makeup flow was such that the matrix seen by the ICP was essentially constant.

SPECTROSCOPIC INTERFERENCES

A review compared high-mass resolution to chemical resolution to resolve spectroscopic interferences when high-precision isotopic ratios are desired (D1). The former is the most straightforward way of resolving many spectroscopic interferences, which is, for example, most desirable for the direct in situ isotopic analysis of solid samples using LA (D1). The same conclusion was reached in a review article on the use of double-focusing ICPMS for the analysis of biological materials (D2). Only in cases requiring resolution settings above 8000 (such as the determination of As and Se in biological samples), does chemical resolution provide certain advantages over DF instruments in terms of sensitivity and detection limits (D2). Chemical resolution may also be a valuable alternative when avoidance of time-consuming sample processing to remove the source of the interference is desired to increase sample throughput and eliminate potential contamination sources (D1). It is achieved through the reaction of the interfering ion with a reaction gas that is introduced in a reaction cell prior to passage in the mass analyzer (D1). Alternatively, the analyte

ion can be transformed through reaction with a suitable gas into a different ion, which no longer suffers from spectroscopic interference. A review on the development and use of collision and reaction cells, including in ICPMS, also concluded that they were most useful for specialized or difficult analytical problems since they can chemically resolve spectroscopic interferences that would otherwise require mass resolutions greater than 600 000 (*D3*).

In fact, the chemical resolution achieved by using H_2 in an octopole collision cell provided higher accuracy and lower uncertainty than double-focusing sector field ICPMS (in medium resolution) for the determination of Ca in human serum by ID using the $^{44}Ca/^{42}Ca$ isotope pair (*D4*). With the collision cell, the removal of spectroscopic interferences from polyatomic ions on the two Ca isotopes was achieved through energy discrimination filtering. This involved selecting the dc offset voltage of the collision cell octopole relative to the quadrupole mass analyzer so that only the higher kinetic energy analyte ions would pass through the quadrupole (*D4*).

Another article reviewed three technologies that can be used to reduce or eliminate spectroscopic interferences arising from ions generated by the plasma gas and the sample matrix (including any solvents or chemicals used for sample preparation): cool (or cold) plasmas, the dynamic reaction cell (DRC), and collision cells (*D5*). These methods were compared as to their suitability for the ultratrace metal analysis of materials used by the semiconductor industry, which demands 10–100 ppt purity levels. For optimum productivity and minimal sample consumption, multielemental analysis with ppt or even sub-ppt detection limits is required. With the cool plasma approach (where the ICP is typically operated at low power and high aerosol carrier gas flow rate), this can only be achieved for a few elements that neither have a high ionization potential nor form refractory compounds. Furthermore, because matrix effects are exacerbated in a cool plasma (which is nonrobust), calibration must often be by the method of standard additions or a matrix-matched external calibration, which is more time-consuming. Although collision cells, where a gas is bled into the cell to collide with polyatomic interfering ions to convert them into noninterfering species, can be used for multielemental analysis, they do not offer sufficiently low detection limits for many elements of interest to the semiconductor industry. This is because light, low-reactivity gases can mainly be used in combination with kinetic energy discrimination (to separate analyte ions from other species), which leads to less efficient interference reduction than what can be achieved with the DRC approach. The latter indeed employs mass filtering (where a quadrupole in the reaction cell is used as a selective band-pass filter) to discriminate against unwanted secondary reaction products. This enables the use of heavier, high-reactivity gases for ion–molecule collisional fragmentation of polyatomic ions, the products of which only need to be different in mass from the analyte ions (*D5*). As a result, although the collision cell and DRC both allow a chemical resolution of spectroscopic interference, the DRC appears to provide more flexibility (*D1*), although the use of heavier gases may increase scattering losses. For example, spectroscopic interferences on S and K were overcome by using of O_2 as a reaction gas in the DRC, which allowed the simultaneous determination of S (as SO^+), K (as K^+), and Zr (as

ZrO^+) (*C39*).

The extent of reaction, which determines the achievable chemical resolution is, in fact, proportional to an exponential of the reaction rate constant. As a result, a difference in reaction rate of the analyte and interfering ion with the reaction gas of 2 or 3 orders of magnitude can yield many orders of chemical resolution (*D6*). For example, all the Pu isotopes could be detected in the presence of at least 6 orders of magnitude higher U concentration using CO_2 as a reaction gas, which oxidized all U^+ and UH^+ but only half of the Pu ions (*D6*). Similarly, Am could be detected in the presence of 3 orders of magnitude greater Pu concentration using NO as a reaction gas (but no single reaction gas was identified that could resolve Pu^+ from Am^+ and from U^+ and UH^+ (*D6*)). In any case, collisional focusing is a beneficial side effect of this approach since the transmission of analyte ions, whether they reacted or not, is often enhanced through collisions with the reaction gas (*D6*).

However, care should be taken to check for side reactions that may either generate other spectroscopic interferences or involve partial reaction with the analyte. This is most critical when ID is used for quantitation as the accuracy of the analysis depends on the analyte isotope ratio accuracy. For example, during the determination of Se isotope ratios from transient signals resulting from a capillary HPLC separation, reaction with H_2 in a collision cell was used to eliminate interferences from Ar dimers (*C82*). In the process, however, some $^{76}SeH^+$ was formed, which interfered with $^{77}Se^+$ being monitored, and had to be corrected for by measuring the ratio of m/z 83 (from $^{82}SeH^+$) over ^{82}Se . The situation was further complicated when other polyatomic ions originating from the sample matrix were not eliminated in the collision cell, such as BrH , which interfered with ^{80}Se and ^{82}Se , and had therefore to be separated by chromatography (*C82*).

In theory, an instrument that would combine chemical and mass resolutions would provide the highest flexibility and the best resolution of spectroscopic interference (*D5*). However, this instrument, which does not yet exist, might be prohibitively expensive. Indeed, the cost of a multicollector (MC) ICPMS instrument is typically 5 times that of a quadrupole-based system or 2.5 times that of a single-collector, double-focusing sector field instrument (*D5*).

A less expensive alternative, which does not require sample pretreatment, i.e., separation of the analytes from the matrix, is through ETV. Not only can in situ sample processing, in particular the pyrolysis step, eliminate sources of spectroscopic (and nonspectroscopic) interferences but ETV provides the ability of temporally separating elements based on their different vaporization temperatures prior to their introduction in the ICP (*D7*). Such temporal resolution can be further increased by using a narrower bore tubing to connect the ETV unit to the ICP. For instance, with a 1.5-mm-i.d. instead of a 6-mm-i.d. transfer line, several isobaric interferences that could not be mass-resolved with high-resolution instruments, such as $^{64}Zn/^{64}Ni$, $^{76}Ge/^{76}Se$, $^{116}Cd/^{116}Sn$, and $^{113}Cd/^{113}In$, could be temporally resolved (*D7*). This increased freedom from spectroscopic interferences came at the cost of decreased sensitivity, which was ~25% of that with a 6-mm-i.d. connecting tube. This is, however, a smaller loss of sensitivity than that experienced on a double-focusing, sector field instrument when going from low- to high-mass resolution, where sensitivity

drops by over 1 order of magnitude.

In addition to resolving many spectroscopic interferences, high-resolution ICPMS can also be used to identify them. For example, it allowed the verification of the incomplete fragmentation of sugar molecules in the ICP (D8). Indeed, the virtually identical high-resolution ICPMS mass spectra from solutions of 3% fructose, glucose, or sucrose contained large polyatomic ions, which were either absent or in much lower abundance with solutions of ethanol and acetic acid, containing nearly identical concentrations of C, H, and O as the sugar solutions (D8). In any case, several examples of approaches that have been used to eliminate spectroscopic interferences are included in Tables 2–5.

NONSPECTROSCOPIC INTERFERENCES

Care should be taken to ensure that methods used to eliminate spectroscopic interferences do not induce nonspectroscopic ones. For example, when using the DRC with ammonia as reaction gas to enable the determination of Cr in whole blood diluted 1:51 (v/v) with a solution containing 0.1 mg/L NH_4OH , 0.1 g/L EDTA, 5 mg/L 1-butanol, and 0.1% Triton X100, significant matrix effects were observed (E1). These nonspectroscopic interferences completely precluded external calibration, even using standard solutions prepared in synthetic matrixes because matrix-matching to whole blood is essentially impossible. Therefore, the method of standard additions had to be used to obtain accurate results (E1). To check that the DRC was indeed the source of the nonspectroscopic interference, V, which can be determined with or without the DRC, was also monitored, which demonstrated that switching the DRC on significantly changed the slope of the calibration curve. Although the slope of water standards was the same as for the blood matrix with the DRC off, they became divergent just as for Cr, when it was switched on, presumably because of additional space charge effects then occurring (E1).

As mentioned in the Sample Introduction section, using micronebulizers operating at low liquid flow rates often results in exacerbated matrix effects compared to those observed for the nebulization of the same solutions at conventional liquid flow rates (i.e., at ~ 1 mL/min) (C9).

The enhancing effect of carbon-containing compounds on Se was evaluated with the high-efficiency, low sample consumption sample introduction system that was described at the beginning of the Sample Introduction section (C4). In combination with a Perkin-Elmer Sciex ELAN 6000, the Se signal was enhanced 5-fold with 40% methanol, 30% acetonitrile, or 35% 2-propanol (C4). Although it was possible to introduce 100% organic solvent without extinguishing the ICP, a total loss of Se signal resulted. In contrast, with the Agilent 7500c (with shield torch and collision cell), only a 2-fold enhancement resulted with 30% methanol, but two-thirds of the Se signal remained with 100% methanol (C4).

When high-throughput trace analysis is required, sector field double-focusing ICPMS in the low-mass resolution mode provides the lowest detection limits. It may be used with a simple dilution of the sample and an external calibration for the highest throughput (E2). The selection of appropriate internal standard(s) and operating conditions is then essential to ensure accurate results. Different internal standards should be tested in a range of matrixes (from standards and samples) to identify the most suitable. The aerosol carrier gas flow rate can then be adjusted

to minimize matrix effects through a comparison of the analyte/internal standard ratio behavior for standard and sample as a function of aerosol carrier gas flow rate, to find the crossover point, i.e., when the ratio is independent of the matrix (E2).

Internal standardization to counteract nonspectroscopic interferences arising from the sample matrix is the most widely used approach to enable high-throughput analysis by external calibration with any type of ICPMS instrument. Although an internal standard is usually selected to match the analyte in terms of mass, a study showed that a combination of internal standards could be even more effective (E3). For example, the use of ^{191}Ir and ^{197}Au provided better compensation of the Pt signal for drift, change in acid concentration, change in rf power, and varying sample introduction rate than the sole use of either Ir or Au. Selection of the best internal standard(s) was based on comparisons of the relative standard deviations (RSD) and relative sensitivity variations before and after internal standardization with one or a combination of internal standards (E3). Such selection could also be based on partial least-squares regression or from a regression of the internal standard intensity versus that of the analyte, the best correction efficiency corresponding to a slope, and a correlation coefficient of 1 (E3).

This author found some comfort in reading that internal standardization with an Ar dimer to alleviate nonspectroscopic interferences, an approach that she proposed in 1987, was being used by a group for the femtogram to microgram per gram multielemental analysis of ice and water samples (E4). However, it being claimed a “novel calibration procedure” was somewhat disturbing! Although this approach can adequately compensate for matrix effects and long-term sensitivity drifts, and has the advantage of not requiring any addition to the sample, which eliminates one possible source of contamination, in this author’s experience, its efficiency depends on the sample matrix and the ICPMS operating conditions. However, it is certainly an option that is worth exploring. The time used to study its efficiency for some sample types on a given ICPMS instrument may be a wise investment if it turns out to be applicable, as it would then significantly increase sample throughput by eliminating a sample treatment step. For a high-salt matrix or when severe drift is encountered, the combined use of internal standardization with the method of standard additions may be required. This was demonstrated in a study with a 500 mg/mL Na matrix and drift induced by drastic changes to the sample uptake rate (E5).

Fundamental Studies. A plasma imaging instrument, which combines Thomson scattering, Rayleigh scattering, laser-induced fluorescence, and computed tomography, was used to determine several fundamental parameters, i.e., electron temperature, electron number density, gas kinetic temperature, and analyte ion number densities (E6). These measurements were made for 0.10 mM Ca, Sr, or Ba solutions containing or not selected concomitant elements (0.01 M Li, Cu or Zn) (E6). The suppression of ion number density and concurrent increase in ion intensity observed for Ca and Sr, without any significant change in the other parameters, suggest that analyte excitation became more efficient in the presence of the matrix element, especially low in the plasma. One possible explanation is that, in the presence of a high concentration of matrix elements, there is a higher probability that high-energy electrons will collide with them, and either ionize

or excite them, than collide with neutral Ar atoms (E6). The leftover energy of the electron after such collision would be too small to ionize Ar or the analyte, leaving just enough energy to excite the analyte ion, leading to enhanced emission but suppressed ion number density.

A review on spatial profiling summarized the valuable information that can be obtained by simply moving the torch, either axially or radially, with respect to the sampling cone (E7). Axial profiling where the plasma is moved away or toward the interface, which is carried out when optimizing sampling depth (albeit often unconsciously!), can provide information on the energy and time needed to form a given ion and hence can indicate matrix-induced earlier desolvation. On the other hand, radial profiling of both analyte and background species, where the plasma is moved across the sampler, can give important information about plasma processes (E7). Indeed, the presence or absence of correlation between profiles of different species can indicate possible interactions within the plasma and, in turn, predominant ionization mechanism(s) in the ICP, and how they change in the presence of a matrix. This information then helps identify the most efficient internal standard(s). However, this approach can be best implemented on instruments that do not suffer from a secondary discharge, i.e., those that do not use some sort of shield between the torch and the induction coil. It should also be preferably carried out using a constant aerosol carrier gas flow rate as a change in the latter can also change the sample introduction efficiency in the plasma. For instance, although axial profiles obtained by varying the aerosol carrier gas flow rate have shown that BaO^+ , Ba^+ , and Ba^{2+} were at increasing heights in the plasma, axial profiles obtained by solely varying the sampling depth under otherwise fixed ICP operating conditions have only confirmed that the oxide species was lower in the plasma; the other two were in fact located in the same region (E7). In any case, monitoring of the axial distribution of the oxide fraction $\text{MO}^+ / (\text{M}^+ + \text{MO}^+)$ has been identified as a simple means of deciphering whether nonspectroscopic interferences occur within the ICP or downstream from it, as only a change in the plasma operating conditions can shift this distribution (E7). Spatial profiling therefore allows one to obtain a more complete picture of nonspectroscopic effects.

For example, a study compared the effect of MeOH or acetone on the signals from analytes spanning the mass range, and with a range of first ionization potentials (E8). However, the whole study was performed under a fixed set of operating conditions, where 1% v/v MeOH enhanced the signals of some analytes (Li, Co, Zn, As, Se) but suppressed others (Rb, Ag, In, Ce, Bi, U) whereas acetone suppressed all signals. The greater volatility of acetone was proposed as the reason for its suppressing effect, where the greater solvent vapor load cooled the plasma (E8). Yet, this would have been clearly evident from a shift of the oxide fraction lower in the plasma, had its axial distribution been monitored. Such spatial profiling might have also shed some light on why carryover from either 7% MeOH or 2% acetone resulted in analyte signal enhancement, especially for As, Se, and Li. Although the enhancement of As and Se was expected from charge transfer with carbon ions, that of light analytes was a spurious effect of their not optimizing at the same position as heavier analytes in the plasma (i.e., a higher aerosol carrier gas flow rate is normally required). Indeed, the introduction of MeOH

induced a shift of the zone of maximum ion density such that light analytes were then sampled at their optimum position (E8). A similar phenomenon likely occurred when a 5- (Y) to 30-fold (Mg, As) enhancement in signal resulted, irrespective of the first ionization potential of the analyte, from merging 20% MeOH at 15 $\mu\text{L}/\text{min}$ with a 340 nL/min sample flow to a micronebulizer (C6).

Another study focused on the selection of robust conditions i.e., operating conditions that reduce the matrix effect from 25 mM Na, 40 mM Al, 25 mM K, 0.5 mM Cs, or 3.0 mM Ba, which induced an average signal suppression, of 20 analytes spanning the mass range, of 10–20% (E9). The effects of aerosol carrier gas flow rate, sample uptake rate, rf power, and ion lens voltage were investigated, individually or in pairs. The first two of these parameters were found to have the most effect on a reduction of nonspectroscopic interferences, with rf power making a more important difference to the level of doubly charged ions, which increased with power (E9). The CeO^+/Ce^+ ratio was, as expected, a good indicator of the robustness of the operating conditions, as it decreased as the robustness increased (E9). Unfortunately, only the average effect on the 20 analyte signals was reported, without any indication of the spread. The authors say that the “robust conditions were universal for all the interferents [sic] in that the optimum was found at the same operating conditions” (E9). However, there is no information on the extent of residual matrix effect for each analyte under these conditions. It is indeed possible that the signal of one analyte would be enhanced while another one is suppressed, resulting in an average elimination of the effect. This has been shown by Beauchemin's group in their numerous studies on nonspectroscopic interferences and their reduction, none of which was quoted by these authors. One cannot help but wonder if the reason for this omission is that the whole picture might not have been as impressive.

Mass bias is one kind of nonspectroscopic interference, where the instrument response is different across the mass range, which affects the accuracy of isotope ratios and, in fact, makes ID a quasi-absolute method with ICPMS, because of the requirement to use a standard to correct for the instrumental mass bias. Sources of mass bias were therefore investigated on two different instruments, multicollector and single-collector, sector field, double-focusing ICPMS, so that appropriate measures could be taken to minimize them (E10). Both of these instruments, which are made by the same manufacturer, have essentially the same sample introduction system, plasma generation system, and interface between the plasma and the mass spectrometer. Although the solution collected from the drain of the spray chamber had an isotopic composition identical to the B solution nebulized, the deposits on the sampler and skimmer had significantly different ones. The deposit on the sampler was enriched in the lighter isotope whereas that on the skimmer was enriched in the heavier one. Grounding the guard electrode did not change the composition of the sampler deposit but increased B fractionation 4-fold in the skimmer deposit (in addition to doubling the amount of deposit outside the skimmer and inducing deposition on its inner surface too) (E10). In any case, this experiment demonstrated that fractionation in favor of the heavier isotope occurred after the sampler cone. Similarly, analysis of Fe, Zn, and Tl deposited on extraction lenses showed a fractionation that was almost linearly

dependent on the mass ratios, which indicated that B fractionation (in favor of ^{11}B) was significantly greater than that found on the skimmer cone with the floating guard electrode (*E10*). This demonstrates that additional fractionation occurred during sampling of the expanding ion beam.

The fact that the deposit on the sampler showed fractionation whereas the solution drained from the spray chamber did not suggests that the ICP itself was a source of fractionation. Radial profiles of the ICP revealed a bimodal distribution of the $^{65}\text{Cu}/^{63}\text{Cu}$ ratio, which suggests that radial diffusion in the ICP contributes to mass bias in ICPMS (*E10*). Furthermore, curve fitting of intensity profiles as a function of sampling depth or aerosol carrier gas flow rate indicated that the maximum ion densities for heavier isotopes were consistently located closer to the torch than those for lighter isotopes of the same element (*E10*). Sampling lower in the plasma, at a position providing 20% of maximum sensitivity, was recommended to minimize changes in mass bias arising from variations in sampling depth as a result of plasma instability, which should improve the precision of isotope ratios. The mass bias was also less dependent on sampling depth with the guard electrode floating, although the sensitivity was then reduced (*E10*). On the other hand, the absolute mass bias was smaller with the guard electrode grounded, as mass bias was then reduced by the increased ion sampling efficiency.

Another group studied the atomization and production of atomic ions from *Bacillus subtilis* bacteria grown in a spiked U medium, which were selected to study the behavior of bacteria in the ICP in view of performing their quantification (*E11*). Analyte (Ca, Mg, U) signal intensity increased significantly as the sonication time was increased to 5 min to lyse bacteria. This indicated that the direct determination of U in intact bacteria by external calibration with inorganic standards would have given negatively biased results by 25 (Ca, Mg) or 31% (U) (*E11*). Perfusion chromatography of U solution, lysed and partially lysed samples, revealed that all the U-incorporated components were released from bacteria by sonication. This therefore confirmed that the ICPMS sensitivity for analyte species in bacteria was lower than that from inorganic standard solution. The direct quantitation of analytes in intact bacteria would thus require a correction if inorganic standard solutions were used for calibration instead of bacterial standards with known amount of analyte (*E11*).

During the continuous nebulization of intact bacteria sample, without separation by perfusion chromatography, positive spikes were noticed in the time-resolved U^+ signal, which were not observed during the continuous nebulization of a U standard solution and suggest that they likely arose from intact bacteria in the ICP (*E11*). This difference in the time-resolved signals of bacteria and standard solutions remained when desolvation of the aerosol was carried out through heater and cooler tubes prior to its introduction into the ICP. However, the signal systematically became substantially noisier with desolvation, for unknown reasons. However, this author thinks that water acts as a buffer in the ICP, and its removal through desolvation exacerbates matrix effects. This is reminiscent of the fact that radial emission measurement in the ICP results in lower matrix effects than axial measurement because the plasma annulus has a damping effect.

A new Cu–Ni laminated cone (Plasmaform) of smaller orifice diameter than a regular Ni cone was found to provide 30–40%

lower sensitivities (commensurate with the reduced orifice diameter) than the regular cone, but with reduced Na-induced signal suppressions, which translated into better long-term stability (*E12*). Suppression, which was dependent on analyte mass, was attributed to salt deposition on the cones (again commensurate with the reduced orifice diameter).

ISOTOPE RATIOS

A study demonstrated that operating conditions should be specifically optimized for isotope ratio measurements, i.e., such as to lower instrumental uncertainties and improve mass bias stability, albeit at the expense of sensitivity and even the absolute level of mass bias (*E10*). Under these conditions, the precision would be best and correction for mass bias more efficient.

Chemical resolution was shown to be more advantageous than using a sector field double-focusing instrument in medium resolution for the measurement of $^{44}\text{Ca}/^{42}\text{Ca}$. Indeed, improved precision for isotope ratio measurements was achieved as a result of collisional damping where the reaction/collision gas, by increasing the residence time of ions in the cell, dampened small-scale fluctuations in the ion beam (*D4*). Furthermore, the lower precision by sector field ICPMS can also be explained by the loss of flat-topped peaks in medium resolution and the fact that the plasma was much less robust, i.e., much more noisy than on the newer collision cell ICPMS instrument used in the comparison (*D4*).

An article reviewed the advantages and limitations of LA-ICPMS for the measurement of isotope ratios directly on solid samples and its application in important areas such as biology, geochemistry, and geochronology (*F1*). The high sensitivity of the double-focusing sector field instrument in low-mass resolution, where flat-topped peaks are obtained, can allow the measurement of isotope ratios with a precision of 0.1% RSD. The simultaneous detection of isotopes on a MC instrument can bring this down to 0.005% (*F1*). As shown in Table 4, cooling the ablation cell with Peltier elements underneath it significantly improved the precision and accuracy of isotope ratios by up to 1 order of magnitude (*C56*). This was attributed to better adsorption of laser energy by the sample at lower temperature, i.e., a more homogeneous spread of laser energy in the sample, which in turn reduced water vapors (*C56*). In fact, this may also eliminate fractionation effects, such as the spontaneous evaporation of low melting point elements from a sample.

The use of ICPMS for the detection of stable isotope tracers in humans was reviewed (*F2*). Stable isotope tracers experiments are often carried out in studies of the metabolism, bioavailability, and requirements and toxicity of elements, both essential and toxic (*F2*). ICPMS is well suited to these studies since it readily allows a quantitation of the shift in isotopic composition induced by the enriched stable isotope through the measurement of the isotope ratio of the tracer isotope over a reference isotope. However, high precision and accuracy is needed so that the small shift can be measured from the natural isotope ratio (often by only 2–6%). The amount of tracer must indeed be kept to a minimum so as not to alter the natural pathways of element absorption and incorporation into the body (*F2*). Quadrupole (with and without collision/reaction cell) and single-collector sector field instruments have been and continue to be used in these studies (*F2*), when a

greater than 0.05–0.1% RSD internal ratio precision is needed (*D1*). With a double-focusing sector field instrument, the precision depends on the mass resolution, the best precision being achieved with flat-top peaks, which are obtained in low-mass resolution (*D1*).

However, manufacturers of multicollector sector field ICPMS instruments have succeeded in preserving the flat-top peak shape at higher mass resolution, hence providing the best precision for isotope ratios while allowing the resolution of many spectroscopic interferences (*D1*, *F2*). In the so-called “pseudo” high-resolution mode, the width of the source slit is reduced by moving one side only, to reduce the proportion of interfering ion entering the mass analyzer, while keeping constant the collector slit so that flat-top peaks are still obtained (*D1*). Isotope ratio precision down to 0.002% RSD can be achieved, therefore allowing the investigation of more subtle isotopic variations (*D1*). The precision in this mode is significantly better than that achieved in high resolution because of the concurrent reduction in sensitivity and disappearance of trapezoidal peak shape (*D1*). On the other hand, multicollector instruments are significantly more expensive than the other types and still require appropriate corrections of mass bias (like all other ICPMS instrument types) (*F2*). The development of multiple collector MS, including ICPMS, was recently reviewed, where emerging applications were highlighted (*F3*). In particular, the hyphenation of MC-ICPMS on-line to LA, GC, HPLC, etc., allows the precise measurements of isotope abundance variations (with appropriate correction for mass bias) for elements with significant roles in biological, geological, nuclear, and chemical processes (*F3*).

In fact, mass bias can often be affected by the concomitant matrix (and even the analyte itself, if its concentration is elevated). For the most accurate and precise isotope ratios, a separation of the analyte from the matrix must still be carried out, the high-mass resolution then being used to resolve the analyte signals from either Ar-containing polyatomic ions or other polyatomic and doubly charged ions from the remaining matrix (*D1*). This separation can be carried out on-line using HPLC, such as that of Nd from Sm (*F4*). However, when doing so, transient signals were generated, across which the isotope ratios were observed to drift with time, as a result of a change in mass bias presumably induced by the mobile phase. Even the injection of a gas mixture containing Kr and Xe revealed a positive drift in their isotope ratio with time, indicating that the heavier isotope was preferentially transmitted through the mass spectrometer (*F4*). Since radioactive isotopes were monitored, correction for mass bias was carried out by normalization to an invariant ratio of the same element. If that is not possible, then an external standard may be used, which will only be efficient if mass discrimination is identical for samples and standards. Using HPLC for the introduction of samples and standards should facilitate normalization to an external standard ratio since the mobile phase then provides a uniform matrix for both (*F4*).

When Fe isotope variation smaller than 1‰/amu was sought, even the residual matrix after Fe extraction by anion-exchange chromatography was sufficient to induce a significant mass bias (*F5*). It was verified that no fractionation of Fe isotopes took place during the separation. To obtain isotope ratios with the best precision, the medium-resolution entrance slit was used and the

detectors were positioned individually to discriminate ArO, ArOH, and ArN at the edge of the detector slit so that only the undisturbed Fe beams would be detected (*F5*). This approach resolved spectroscopic interferences by less than $4000M/\Delta M$ while producing flat-top peaks and, hence, high-precision isotope ratios. To obtain the most accurate ratios, the actual mass bias law should be established by plotting $\ln(^{56}\text{Fe}/^{54}\text{Fe})$ versus $\ln(^{57}\text{Fe}/^{54}\text{Fe})$ for samples and standards over time, as the exponential law and the power law are both empirical, and the actual law varies from instrument to instrument. Two usual means of correcting for mass bias were also compared. Sample–standard bracketing assumes that the mass bias is identical for samples and standards, i.e., that it is stable with time and not affected by matrix effects. It is only suitable if a thorough purification is done. Otherwise, as was observed in this study, a significant difference in $\delta^{56}\text{Fe}/^{54}\text{Fe}$ may result from the significantly different mass bias observed with standards than with samples (*F5*). On the other hand, adding a spike element to all samples and standards whose mass is similar to that of the analyte assumes that the mass fractionation is the same for the analyte and spike elements. However, even when the mass fractionation was different, this approach yielded more precise and accurate results than the bracketing approach if the mass fractionation was constant. Indeed, with constant mass biases, a plot of $\ln(^{56}\text{Fe}/^{54}\text{Fe})$ versus $\ln(^{65}\text{Cu}/^{63}\text{Cu})$ (the spike element) for samples and standards yielded parallel linear arrays, with $\delta^{56}\text{Fe}/^{54}\text{Fe}$ being the vertical distance between them. Using this regression method, $\delta^{56}\text{Fe}/^{54}\text{Fe}$ with 0.03–0.11‰ (2 σ) external reproducibility was obtained (*F5*).

Even with two separations to obtain a high-purity U fraction, several precautions had to be taken to ensure high-precision $^{234}\text{U}/^{238}\text{U}$ by MC-ICPMS (*F67*). A U metal SRM, which was used to optimize sensitivity and achieve aligned flat-topped peak shapes for the three natural U isotopes, was also used as a bracketing standard to correct all measurements for mass bias, using an exponential mass fractionation law (*F6*). To avoid having to determine dead time accurately and precisely, and to reduce the effect of nonlinearity in the response of the discrete dynode electron multiplier variable intensities, count rates for ^{234}U were kept below 1×10^5 counts/s (*F6*). Memory effects, from leftover U-rich droplets in the spray chamber and desolvation system, were minimized by heating the entire spray chamber to 70 °C. An alternative approach to the conventional multiple Faraday cups and electron multipliers was also proposed. It simply involved multiple Faraday cups, where the preamplifier connected to the ^{238}U Faraday cup was fitted with a $10^9\Omega$ resistor (instead of the regular $10^{11}\Omega$) to enable the simultaneous Faraday cup measurements of ^{238}U , ^{235}U , and ^{234}U in the same analysis sequence (*F6*). Either approach provided precision at the level of 1 part in 10^4 , but the former one consumed ~120 ng of U and took 75 min/measurement, whereas the latter required 2 min and 400–650 ng/analysis (*F6*).

Despite the high-precision isotope ratios obtained with MC-ICPMS following extensive matrix separation and with adequate corrections for mass bias and dead time, several people are already asking for modifications by manufacturers. For example, more discrete dynode electron multipliers would have been preferred by one group to allow the simultaneous detection of all weak U isotopes within one measurement sequence as this would have

shortened the analysis time (*F6*). It would have also precluded a physical modification of the detection system (i.e., change of the resistor on a Faraday cup) that was attempted to enable this simultaneous measurement (*F6*). Another group, who studied Mo isotopic variations in freshwater sediment columns and in molybdenites, had to sacrifice ^{92}Mo due to mechanical limitations in the positioning of collectors for wide mass coverage, which only allowed the measurement of six Mo isotopes in addition to the two Pd isotopes required for mass bias correction (*F7*).

If an invariant isotope ratio of the analyte can be used as an internal standard, then correction for mass bias, drift, and matrix effects will be accomplished. This was demonstrated for the measurement of $^{87}\text{Sr}/^{86}\text{Sr}$ in natural waters (river, tap, ocean, brines) and carbonates, where precision of 0.002% (2σ) was achieved with up to 500 mg/L total dissolved solids without matrix separation, using $^{86}\text{Sr}/^{88}\text{Sr}$ as internal standard since it is constant in nature (*F8*). In fact, the accuracy and precision achieved were identical to those obtained after matrix separation. Similar results were obtained using of $^{235}\text{U}/^{238}\text{U}$ as internal standard for $^{234}\text{U}/^{238}\text{U}$ and even with $^{205}\text{Tl}/^{203}\text{Tl}$ as internal standard for Pb isotope ratios (*F8*). However, when $^{61}\text{Ni}/^{62}\text{Ni}$ was used as an internal standard for $^{65}\text{Cu}/^{63}\text{Cu}$, an appropriate correction for drift and the matrix effect from 10 mg/L Fe was achieved but not for the matrix effect from 10 mg/L Pb (*F8*). Nonetheless, the use of an appropriate internal standard is invaluable as it eliminates the need for matrix separation procedures, hence minimizing the chance of contamination, and for sample–standard–sample bracketing, which is time-consuming.

When using another element as internal standard to correct for mass bias of an analyte, care should be taken to ensure that this element does not undergo redox reactions or that the different redox species behave similarly during sample introduction. For example, Tl⁺, which can be oxidized to Tl³⁺ by solar UV radiation, behaved differently from the latter during desolvation, which consistently resulted in higher measured Pb/Tl and $^{205}\text{Tl}/^{203}\text{Tl}$ ratios (*F9*). Such problem could be eliminated by either analyzing sample solutions right away (i.e., within 1 h of their preparation) or by keeping them in the dark (*F9*).

Yang and Sturgeon compared six different mass bias correction models for the determination of Hg isotope ratios using Tl, Os, or Ir as internal standard: the linear law, power law, exponential law, Russell equation, common analyte internal standardization (CAIS), and polynomial function (*F10*). The power law and exponential law in combination with $^{203}\text{Tl}/^{205}\text{Tl}$ as internal standard gave a smaller relative difference between the measured isotope ratio and the expected one from IUPAC values than did the linear law. The other two internal standards (i.e., $^{191}\text{Ir}/^{193}\text{Ir}$ and $^{190}\text{Os}/^{192}\text{Os}$) were less efficient than Tl for mass bias correction (*F10*). An even lower relative difference was obtained using Tl and the Russell equation because the latter depends on the absolute masses of the isotopes in the ratio. With CAIS, which requires a minimum of two isotope ratios from one or more internal standard, whose isotopes have the same mass difference as those of the analyte, the relative difference was greater than those obtained with the power law, exponential law, and Russell equation. The polynomial model, which is based on a second-order polynomial instrumental response function, in combination with three internal standards (Tl, Ir, Os) provided the smallest relative difference of

all six models (*F10*). This conclusion was reached for the sector field double-focusing ThermoFinnigan Element2 in low resolution. The best correction model may be different on other ICPMS instruments and should therefore be checked.

There is an additional requirement for performing appropriate correction for mass bias and dead time to obtain accurate and precise isotope ratios from very fast transient signals, such as those obtained by capillary HPLC where the baseline full width is ~ 15 s. Indeed, the measurement conditions should be selected such that 20 data points can be obtained across the peak to provide an adequate peak profile (*C82*). This means that on sequential detectors, such as quadrupole or single-collector sector field instrument, the integration time per isotope will be low. A degradation of precision is therefore expected compared to that obtained for isotope ratios measured by continuous nebulization because a longer integration is possible in the latter mode.

Krupp and Donard investigated the drift in Pb and Hg isotope ratios that they observed during the short transient signals generated by capillary GC coupled to different MC-ICPMS systems (*F11*). No change in instrumental mass bias, chromatographic fractionation effect, inappropriate background correction, or influence from the analyte concentration could be found. On the other hand, a dependence on peak width was clearly shown, i.e., the relative change in analyte concentration as a function of time, which was more pronounced as the transient signal became narrower (*F11*). The fact that similar effects were observed on different MC instruments suggests that the reason is linked to the instrument design, and very likely the detection system, which was designed for continuous, not transient, signals.

The same group also developed a special peak integration method for cases when the transient peak is not perfectly symmetrical and peak tailing occurs, as the definition of the start and end of the peak then introduces uncertainties in isotope ratios that are obtained by taking the ratios of peak areas, which degrade the precision that would otherwise be achievable by MC-ICPMS (*F12*). The method simply involves integration, using a trapezoidal rule, only in the region where the point-to-point isotopic ratio is constant. This approach improved the precision of S isotope ratios in GC peaks by factors of 2.5–15 compared to that achieved with classical peak area integration (*F12*). It is applicable to any technique generating transients signals subject to peak tailing (GC, LA, FI, etc.).

The measurement of isotope ratios from transient signals generated by flow injection with either quadrupole or axial TOF-based ICPMS was studied by Beauchemin (*F13*). The ratio of peak areas and the averaged point-to-point ratio were computed for different full-width (FW) windows at different fractions of maximum height and different time windows centered on the peak maximum. The time-window approach was found to be more dependent on the assignment of the start and end of the transient peak than the FW approach. With quadrupole ICPMS, the accuracy of isotopic ratios was mostly independent of the window whether the ratio of peak areas or averaged point-to-point ratio was calculated. However, better precision was obtained than by either continuous nebulization or calculating the ratio of peak heights of the transient peak, which suggested mass discrimination during sampling. No such systematic difference in precision was observed with ICP-TOFMS where, however, ions are acceler-

ated to high kinetic energy prior to their admission in the flight tube (*F13*). Since only three ratios ($^{57}\text{Fe}/^{56}\text{Fe}$, $^{65}\text{Cu}/^{63}\text{Cu}$ and $^{68}\text{Zn}/^{64}\text{Zn}$) were monitored by quadrupole ICPMS, an expanded study is warranted to verify if better precision using partial windows of FI peaks would be similarly observed for isotopic ratios across the mass range. On the other hand, the accuracy of ratios measured by ICP-TOFMS was degraded compared to that by quadrupole ICPMS, especially in regions near deflection windows (which must be used to prevent abundant ions such as Ar and ArO, from continuously striking the detector in axial ICP-TOFMS). Furthermore, although better precision was systematically obtained using point-by-point ratios rather than taking the ratio of integrated signals when continuous nebulization was done, this difference, which was not observed with a quadrupole ICPMS, vanished in the FI mode (*F13*). Given the number of sample introduction approaches that generate transient signals, during which isotopic ratios must be measured (to, for example, implement the powerful ID approach), more studies are warranted on all ICPMS instruments to determine the window providing the most precise isotopic ratios.

Isotope Dilution. Schaumlöffel and Łobiński reviewed the use of ID for the quantitative determination of metallo(id)biomolecules in biological systems (*F14*). For unknown biomolecules, species-unspecific ID can be done, where an isotopically labeled spike of the analyte is continuously added after the separation of the analyte species. For known compounds, species-specific ID can be carried out, where an isotopically labeled analyte species is added to the sample prior to the separation of analyte species. In both cases, equilibration of the isotopically labeled spike with the sample is a prerequisite. In the latter case, the absence of isotope exchange between different species is also required. However, if these constraints can be met then an ideal internal standardization is accomplished, resulting in correction for incomplete recoveries and matrix effects. A huge advantage of ID loss of analyte after the isotope dilution step (including equilibration) through, for example, incomplete extraction or partial volatilization does not affect accuracy. This feature is however fully realized if the spike/reference isotope ratio can be suitably corrected, especially for mass bias, which is more easily accomplished on low-mass resolution than on high-resolution instruments (*F15*). The largest impediment to the routine application of ID-ICPMS to speciation analysis is the limited availability or unavailability of isotopically labeled compounds (*F15*). However, species-specific ID allows a validation of speciation methods since it can follow species transformations without jeopardizing accuracy, which cannot be readily performed by other methods (*F15*, *C82*). However, care should be taken to verify that the isotopically labeled spike does not react before the isotopic equilibrium is reached with the analyte in the sample, as the accuracy of the analysis would then be jeopardized (*C82*).

As a result of the great accuracy and precision arising from the use of ID-ICPMS, an increasing number of ICPMS users are implementing it. To further facilitate this process, a tutorial review has even been written on how to do ID analysis, especially for elemental speciation analysis (*F16*). This review also includes numerous examples of application of species-unspecific, species-specific, and even speciated ID, where multiple spikes are used to correct for species interconversion reactions (*F16*). On the

other hand, when a laboratory of chemical metrology had several laboratories implement ID to test if it could be considered a reference method, the results were, on average, not much better than those obtained by more conventional methods (*F17*). This modest performance was attributed to the inexperience of the majority of participants with ID and ICPMS. Yet, if a double ID is done, where a reverse ID of the isotope spike solution is made prior to the ID of the sample because the spike concentration can vary with time, a total uncertainty of 1–5% can typically be obtained whatever the analyte concentration (*F17*). This makes ID most valuable for the determination of trace elements (i.e., where concentration is $\leq \mu\text{g/L}$) (*F17*).

INSTRUMENT PERFORMANCE

A product review reported that, according to sales representatives, 86% of ICPMS instruments sold are quadrupoles, whereas 13% are sector field instruments, and only 1% are TOF machines (*A1*). This distribution is not surprising since the quadrupole types are the least expensive and simplest and have been around for the longest time, so they are more robust than the other two types. In fact, the sales of TOF instruments may go further down since, at the time of writing, only one manufacturer is marketing ICP-TOFMS. LECO Corp. (one of the two manufacturers mentioned in the article) has stopped advertising their product (including on their web site). Analytik Jena, which was expected to market an instrument (*G1*), is still working on it. Convincing potential buyers that a sacrifice of ~ 1 order of magnitude in sensitivity (compared to quadrupole instruments) or more (compared to sector field instruments in the low-resolution mode) is worth it for the multielemental and multi-isotopic analysis of fast transient signals should therefore be more difficult. The multichannel feature of ICP-TOFMS, which allows the entire mass range to be monitored (*G1*), really becomes an advantage over the other types of ICPMS instruments only when either a large number of analytes must be monitored or information is required on unknown or unexpected species. One example of such application is the determination of expected and unexpected elements during the laser ablation of fluid inclusions in geological materials (*G1*), where this information must often be obtained during a single LA shot.

Another review pointed out that its extremely rapid data acquisition makes ICP-TOFMS highly competitive to sequential ICPMS such as quadrupole-based instruments, because it allows one to obtain qualitative and quantitative information in a very short time that is independent of the number of isotopes monitored (*G2*). Because of its inherently lower duty cycle resulting from the requirement to modulate the ion beam, its achievable sensitivity and detection limits are often degraded by 1 order of magnitude compared to those obtained by ICP-QMS. However, this disadvantage can rapidly disappear when several isotopes must be monitored, as the duty cycle of any scanning mass analyzer then diminishes while that of ICP-TOFMS remains unchanged (*G2*).

The status of array detection for MS was reviewed (*G3*). Improvements in the performance of array detectors would have a significant impact on the quality of MS results. Indeed, the simultaneous detection of ions having different m/z ratios allows improved detection limits as well as improved precision through

elimination of correlated noise sources by using the ratio and a reduction in sample consumption, which in turn leads to a shorter analysis time and, hence, a higher sample throughput.

Whatever the type of instrument used, the range of concentrations used for external calibration may affect the measurement uncertainty, especially when low concentrations are being determined. For example, during the determination of Pt in biological fluids, the uncertainty component associated with the repeatability was found to be constant over the analyte concentration range, while the sampling uncertainty was negligible (G4). On the other hand, the uncertainty component due to the external calibration (with internal standardization using Ir) increased significantly as the analyte concentration decreased, especially at the lowest concentrations (G4). The study demonstrated that the most precise results were obtained when the analyte signal was close to the centroid of the signal versus concentration regression line, which could be achieved by reducing the calibration concentration range or increasing the number of calibration points (G4). A similar conclusion was reached from the peak areas of transient signals resulting from either FI or liquid chromatography (G5). However, a simple two-point calibration was recommended as the most cost-effective external calibration for speciation analysis, since it maximized sample throughput by minimizing the time required for calibration between chromatographic runs (G5).

Another study demonstrated that, from a statistical point of view, multiple-point calibration did not provide better results than a two-point calibration, i.e., with a blank and a single standard solution (G6). The latter indeed avoids the uncertainty associated with fitting a regression model to the data. However, with a multiple-point calibration, where a weighed linear regression model is recommended because residuals and uncertainties at the low end of the calibration tend to be lower than using a simple regression, gross errors in the preparation of standard solutions or malfunction of the instrument may be easily identified (G6).

Problems encountered during the routine analysis of large numbers of numerous samples (including sediments, soils, milk, milk products, blood, vegetation, and animal tissues) were reviewed (G7). Various sources of uncertainties were discussed, from inadequate sample preparation to the measurement steps. With an ultrasensitive technique such as ICPMS, measurable blanks result. The importance of preparing numerous method blanks (i.e., 10–25), where all the sample preparation steps are followed without the sample, to check if they exhibit significant variation was stressed (G7). Indeed, reproducible blanks indicate that sources of contamination are under control and reproducible, which enables subtraction of the blank mean from sample results. The selection of a suitable internal standard, which is not present in the sample and is efficiently correcting analyte signal for drift and matrix effects, is often difficult when numerous analytes have to be monitored. Dilution is therefore recommended as much as possible to minimize matrix effects, without diluting so much that the blanks become significant. Monitoring the analyte concentration found for various dilution factors of a sample solution provides a simple means of studying of the extent of matrix effects (G7). The dilution factor where these effects become negligible is indicated when the same analyte concentration is obtained for more dilute sample solutions.

Diane Beauchemin received a B.Sc. in chemistry from l'Université de Montréal and then a Ph.D. in analytical chemistry from the same institution at the end of 1984 (under the supervision of Joseph Hubert). After working as a Research Associate in the Institute for National Measurement Standards of the National Research Council of Canada, she moved to Queen's University in 1988 and was eventually promoted to Full Professor (in 2001). She is interested in all aspects of ICPMS, from fundamental studies on matrix effects and mixed-gas plasmas to environmental and biomedical applications (including chemical speciation analysis and the determination of bioaccessibility).

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