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Recent developments in isotope analysis by advanced mass spectrometric techniques†
Plenary lecture

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An outstanding feature of mass spectrometry is the possibility of determining exact masses and accurate abundances of stable and unstable isotopes with high precision. The importance of isotope ratio measurements by mass spectrometry has grown in the last few years due to a significant improvement of instrumentation with respect to sensitivity, detection limits, precision and accuracy, whereby especially the determination of very small abundances of stable isotopes and radionuclides at the ultratrace concentration level is of increasing importance. The improvement of mass spectrometers for isotope ratio measurements with respect to more efficient and powerful ionization techniques, improved ion separation systems and especially the development of sensitive ion detectors using single ion and multiple ion collectors with increased abundance sensitivity has been accelerated by the necessity of obtaining the most precise and accurate isotope ratio data from the smallest possible amount of sample. Advancement in the determination of stable isotopes and long-lived radionuclides at very low concentration levels and low abundances has been achieved for environmental monitoring, the study of isotope variation in nature and in environmental science, in geoscience (geochemistry and geochronology), cosmochemistry and planetary science and in nuclear science (for the quality assurance of fuel material and for radioactive waste control) *etc.* Important progress has been obtained in the refinement of the variable multiple collector system in MC-ICP-MS, improvements in current amplifier technology to achieve ultimate precision and accuracy, increased abundance sensitivity, improved ion optics using zoom optics, enlarged geometry of mass spectrometers and increased signal to noise ratios. This review focuses on methodological and instrumental developments, novel approaches and different applications in isotope ratio measurements using different mass spectrometric techniques such as ICP-MS (inductively coupled plasma mass spectrometry) and LA-ICP-MS (laser ablation ICP-MS) *versus* TIMS (thermal ionization mass spectrometry), AMS (accelerator mass spectrometry), RIMS (resonance ionization mass spectrometry) SIMS (secondary ion mass spectrometry) and GDMS (glow discharge mass spectrometry). This review can be regarded as a follow-up to a previous review by the author on a similar topic: J. S. Becker, *J. Anal. At. Spectrom.*, 2002, **17**, 1172 (ref. 2).

Dr. habil. J. Sabine Becker is currently head of the mass spectrometric group of Central Division of Analytical Chemistry, Research Centre Juelich, Germany. Her research activities are focused on trace, ultratrace, isotope and surface analysis using different inorganic mass spectrometric methods (such as ICP-MS, LA-ICP-MS, TIMS, SSMS, LIMS, GDMS, SIMS and SNMS). Her current research interests are in the development of highly sensitive methods for trace, ultratrace and isotope analysis in environmental, biological and materials research, in life science, medicine and bioengineering by ICP-MS and LA-ICP-MS. Other major research topics are the ultrasensitive determination of long-lived radionuclides for the characterization of radioactive material and environmental monitoring and especially the development of LA-ICP-MS for micro- and nanolocal distribution analysis in medicine and life science, e.g., for quantitative imaging of elements on brain tissues using solution based calibration, and development metallomics and phosphoproteomics by LA-ICP-MS in combination with MALDI-FTICR-MS in cooperation with the University of Konstanz. She is author and co-author of 250 scientific publications, of about 560 lectures, a Board member of the "German Applied Spectroscopic Society" (DASp) and "German Society of Mass Spectrometry" (DGMS) and a member of, inter alia, the International Advisory Boards of the International Journal of Mass Spectrometry and the Journal of Analytical Atomic Spectrometry.

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1. Introduction

For many decades atomic mass spectrometry has occupied an outstanding position among the analytical techniques due to its universality, high sensitivity and wide fields of application in elemental analysis, especially in the determination of trace and ultratrace elements.[1,2] One of the main characteristics of mass spectrometry is the possibility of precise and accurate isotope ratio measurements. Because the isotope abundances of several elements are not constant and vary as a result of nuclear, biological, chemical, geochemical and physical processes isotope analysis is necessary for quite different fields of research and applications. For example, isotope ratio measurements are required for the study of natural isotope variation,[3–9] for age dating of rocks,[10] for determination of the origin of foods, plants or minerals, for the characterization of nuclear samples and radioactive waste control,[11,12] for environmental monitoring[13–15] or characterization of medical samples (blood, urine, faeces, hair and tissue analysis) for health control, also of exposed persons,[16–19] for analysis of biological materials[20] and a number of other applications. Also tracer experiments and the isotope dilution technique using enriched stable isotopes would not be thinkable without mass spectrometry.[21–27] Precise isotope ratio measurements of artificial radionuclides in environmental samples are helpful for evidence of environmental contamination and to evaluate the sources.[28–30]

For measurements of isotope ratios or abundances any mass spectrometer with one of the following types of ion sources (electron beam, secondary ion source, spark source, glow discharge source, laser ion source, inductively coupled plasma ion source) can be applied. Old mass spectrometric techniques such as spark source mass spectrometry (SSMS) and laser ionization mass spectrometry (LIMS) were replaced many years ago by glow discharge mass spectrometry (GDMS)[31] and laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS),[32] respectively, for the direct isotope analysis of solid samples. Glow discharge ion sources have been used in inorganic mass spectrometry for more than 50 years especially for trace element analysis and depth profiling in solid samples. But GDMS has also been applied for isotope analysis in samples of nuclear concern in Betti's group.[31,33] Besides GDMS, SIMS (secondary ion mass spectrometry) as a powerful surface analytical technique (*e.g.*, for depth profiling) is also suited for precise isotope ratio measurements on solid samples. Due to the high lateral resolution possible in the µm range and below as an *in situ* technique (in the ion microprobe mode) SIMS provides the possibility of measuring isotope ratios directly within single mineral grains without any sample preparation.[31]

Other mass spectrometric techniques such as resonance ionization mass spectrometry (RIMS)[34–37] and accelerator mass spectrometry (AMS)[3,38–40] possess high isotope selectivity for an extreme ultratrace and isotope analysis of, in particular, radiotoxic isotopes (^{14}C, ^{41}Ca, ^{90}Sr, ^{99}Tc, ^{210}Pb, ^{236}U and plutonium isotopes) in the environment, cosmochemistry, radiodating, nutrition and biomedical research. Resonance ionization mass spectrometry (RIMS) has become as an ultrasensitive and selective analytical technique for the determination of extremely low isotope abundances.[34,37,41] Recently, Wendt and Trautmann[42] reported on developments in isotope ratio measurements by RIMS. In spite of excellent analytical features of RIMS (detection limit for isotopes: 10^6 atoms per sample) and exciting applications for the determination of extremely low abundances and isotope ratios of long-lived radionuclides such as all plutonium isotopes (including ^{238}Pu), ^{236}U or ^{41}Ca, no commercial instrument is available on the analytical market.

Accelerator mass spectrometry (AMS), developed in 1977 by introducing accelerators (cyclotron[43] and tandem accelerator[44]) into mass spectrometry, is the most powerful, sensitive and selective mass spectrometric technique for measuring long-lived radionuclides at the level of natural isotopic abundances (10^{-16} to 10^{-12}).[3,38,39,44] For isotope analysis—especially for long-lived radionuclide analysis, such as ^{41}Ca determination at the natural level, $^{41}\mathrm{Ca}/^{40}\mathrm{Ca} = 10^{-14}$–$10^{-15}$—AMS is the method of choice at the extreme ultratrace level. The minimum detectable isotopic ratio for $^{129}\mathrm{I}/^{127}\mathrm{I}$ of about $<10^{-12}$ can be only achieved by AMS.[45] The dominant field of AMS is ^{14}C measurements for age dating in archaeology, geology, geophysics and other sciences.[3] However, RIMS and AMS involve complicated and expensive experimental equipment and the analysis, including sample preparation, is time-consuming.

Thermal ionization mass spectrometry (TIMS) as a reliable and selective isotope analytical technique in routine work for high-precision isotope ratio measurements is used in many laboratories worldwide for precise isotope ratio measurements especially for elements with ionization potential <7 eV,[1] such as alkali and earth alkali elements or rare earth elements (REE). Electron impact (EI) mass spectrometry, which similar to TIMS produces near-monoenergetic ions, is an excellent tool for the high-precision isotope analysis of selected elements (especially for light elements such as H, C, N and O but also for S or Si).[6,46,47] Electron impact ionization combined with mass spectrometry has been applied for elements which readily form gaseous compounds (*e.g.*, CO_2 or SO_2 for the isotope analysis of carbon and sulfur, respectively). Obviously, a large proportion of the papers applied isotope ratio mass spectrometers with electron beam ionization for the analysis of gases: this technique will not be discussed in this review.

For a couple of years now the most widely used mass spectrometric technique is inductively coupled plasma mass spectrometry (ICP-MS) with single and multiple ion collection, which allows isotope ratios to be measured in a short time with good accuracy and precision.[2,48] ICP-MS as a powerful and universal tool has opened up new applications for isotope ratio measurements of elements also with a high first ionization potential, which are difficult to analyze with TIMS (such as Mo, Hf, Fe). For direct isotope ratio measurements on solid samples laser ablation ICP-MS (LA-ICP-MS) is applied to an increasing extent in geology, geochronology, biology and environmental research as reviewed by Pickhardt *et al.*[32] Of all the different mass spectrometric techniques for isotope analysis (such as ICP-MS, LA-ICP-MS, TIMS, GDMS, AMS, SIMS, RIMS and isotope ratio mass spectrometry of gases) the greatest proportion of published papers concerns ICP-MS with single and multiple ion collection due to the widespread use of ICP mass spectrometers, the multielement capability, very low detection limits, and good accuracy and precision of measurements.[2] Of all the heavy metals studied uranium was favored by ICP-MS.

The aim of this article is to review recent developments in isotope ratio measurements by advanced mass spectrometric techniques.

Mass spectrometric techniques and instrumentation

As the most frequently used atomic mass spectrometric technique, ICP-MS is applied for fast and relatively inexpensive multielement determination, for speciation and for precise and accurate isotopic analysis at the trace and ultratrace concentration levels in any material. In contrast to RIMS and AMS, ICP-MS is very advantageous due to the relatively low costs and high sample throughput, which is especially required for environmental, nuclear or medical controls.[16,17,28,49–51] Another advantage of ICP-MS compared to all other atomic mass spectrometric techniques is the mostly simple sample preparation (*e.g.*, by microwave-induced digestion of solid samples) and the introduction of aqueous solutions into the inductively coupled plasma of a normal pressure inductively coupled plasma ion source (ICP).

Several types of quadrupole-based ICP-MS with and without a collision cell (*e.g.* from companies such as Perkin Elmer Sciex, Agilent, Thermo Electron, GV Instruments, Varian *etc.*) were used in isotope ratio measurements. In general, quadrupole-based ICP-MS without a collision cell allows isotope ratios to be measured in a few minutes by a routine method with a precision (RSD—relative standard deviation) between 0.1 and 0.5% and detection limits in the pg mL^{-1} range and below in aqueous solutions. This precision is sufficient for several applications, *e.g.*, for evidence of contamination of urine with natural, depleted or enriched uranium (this technique is used in the author's laboratory in a routine mode[52]) or use of the isotope dilution technique for the quantitative determination of trace element concentration with the aid of enriched isotope spikes.

An important limiting factor—which deteriorates the accuracy and precision of the isotope analysis—is the occurrence of isobaric interferences of analyte ions with atomic ions or molecular ions at the same m/z ratio. The precision of isotope ratio measurements and the detection limits for selected elements, in particular elements which are difficult to determine due to the appearance of isobaric interferences (*e.g.*, by the isotope ratio measurements of Ca, Fe, S, I and Se),[30,53–58] was improved by the insertion of a collision/reaction cell in quadrupole-based ICP-MS. By the collisions of ions formed in the ICP with gas atoms (He, Xe, Ar) or molecules (H_2, O_2, CH_4, NH_3) introduced into a collision cell of ICP-MS the kinetic energy spread of ions is reduced from several eV to <0.1 eV, which results in an increasing sensitivity of analyte ions, *e.g.*, U.[56–58] Furthermore, by the reaction of the collision gas with ions in the collision cell possible isobaric interferences by disturbing atomic or molecular ions were reduced significantly. For example, a determination of $^{80}Se^+$ or $^{40}Ca^+$ isotope abundance, which is problematic or impossible using sector field ICP-MS even at high mass resolution, can be advantageously performed by ICP-QMS with a collision cell because the interfering argon dimer ions ($^{40}Ar_2{}^+$) were dissociated or atomic plasma gas ions ($^{40}Ar^+$) were neutralized *via* collision-induced reactions (using a mixture of He/H_2 or NH_3 as the collision gas).[53,54] However, molecular ions were also formed in the collision cell and these can be used as analyte ions. For example, $^{31}P^+$ or $^{32}S^+$ determination is carried out *via* the oxide ions $^{31}P^{16}O^+$ and $^{32}S^{16}O^+$, which are interference-free at $m/z = 47$ and 48, respectively, formed with maximum ion intensities in the collision or reaction cell under optimized experimental condition.[59]

Several quadrupole-based ICP-MS with collision/reaction cells are available on the analytical market, *e.g.*, with a hexapole collision cell (ICP-CC-QMS, Platform, GV Instruments formerly Micromass), with a quadrupole dynamic reaction cell (Elan 6100 DRC from Perkin Elmer) or octopole reaction cell (ICP-ORC-MS from Agilent). A precision for ^{82}Se/^{80}Se and ^{40}Ca/^{44}Ca isotope ratio measurement of 0.20 and 0.26%, respectively, was obtained by ICP-CC-QMS (Platform, Micromass).[2] Recently, GV Instruments replaced the linear hexapole collision cell for collision-induced reactions and ion thermalization and ion focusing in the Platform ICP-CC-QMS by a dual axis hexapole collision cell (Platform XS, VG instruments, Fig. 1[60]) as a more efficient and maintenance-free neutrals/photons filter. Using this experimental arrangement, the background signal could be reduced by nearly one order of magnitude compared to the old arrangement with a linear hexapole collision cell. For example, an isotope ratio on NIST SRM U050 of $^{235}U/^{238}U = 0.052784 \pm 0.00012$ was measured with the ICP-CC-QMS Platform XS.[60]

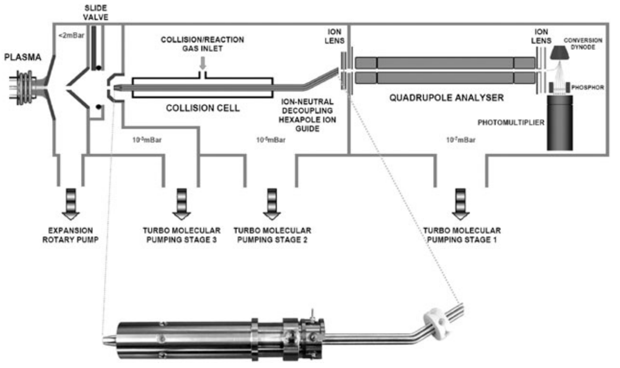


Fig. 1 Experimental arrangement of quadrupole-based ICP-MS with dual axis hexapole collision cell, Platform XS (GV Instruments, Manchester)[60] (reproduced with permission of GV Instruments, with acknowledgement to H. Read).

A frequently applied ICP-mass spectrometer in isotope analysis is the double-focusing sector field instrument ELEMENT from Thermo Electron. The experimental arrangement of the ICP-SFMS ELEMEMT with reverse Nier Johnson geometry is shown in Fig. 2. ICP-SFMS allows a determination of isotope ratios with a precision between 0.02% (at low mass resolution: $m/\Delta m \sim 300$) and 0.2% (at medium mass resolution: $m/\Delta m \sim 4000$) and detection limits at pg mL^{-1} to the sub-fg mL^{-1} range. Recently, Thermo Electron improved the ion detection system of the market leader ICP-SFMS ELEMENT (called: ELEMENT XR) and extended the dynamic range up to $\sim 10^{12}$.[61] This performance combined with an improvement of abundance sensitivity is relevant for simultaneous matrix and ultratrace analysis and would be of importance in the isotope analysis of extremely small isotope ratios for future applications.

To overcome the limitation of the mass spectrometer with a single ion collector (*e.g.*, plasma instabilities—so-called "flicker noise"—or mass drift effects) multiple ion collector mass spectrometry for simultaneous measurements of mass-separated ion currents of several isotopes have been developed. The precision for isotope ratio measurements was improved in sector field mass spectrometers down to 0.001–0.002% when multiple ion collectors (MC) for the simultaneous detection of mass-separated ion currents were inserted. For example, Plasma 54 from VG Elemental, Nu Plasma from Nu Instruments, Isoprobe from GV Instruments and Neptune from Thermo Electron ICP-MS with multiple-ion collectors (MC) are the most precise ICP mass spectrometers available today. The Plasma 54 (VG Elemental) was the first MC-ICP-MS (with nine Faraday collectors and a single Daly detector for ion counting) on the analytical market developed from the Sector 54 TIMS (VG Elemental) 20 years before. The experimental setup of several MC-ICP-MS is shown in Fig. 3. The multiple ion collector ICP mass spectrometers VG Plasma 54, Nu Plasma and Neptune are constructed as double-focusing sector

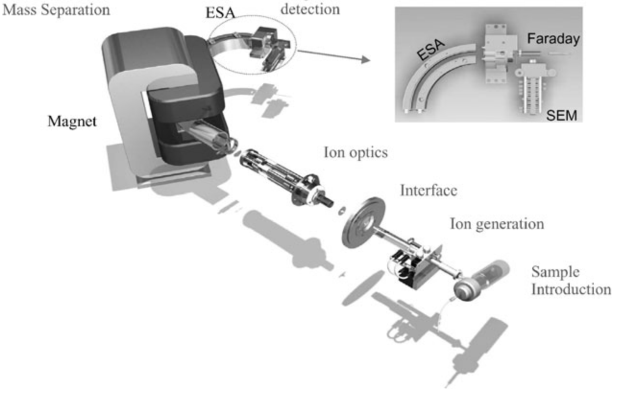


Fig. 2 Double-focusing sector field ICP-MS (ICP-SFMS, ELEMENT XR, Thermo Electron, Bremen) with extended dynamic range ($\sim 10^{12}$). Reproduced by permission of Thermo Electron, with acknowledgment to M. Hamester.[61]

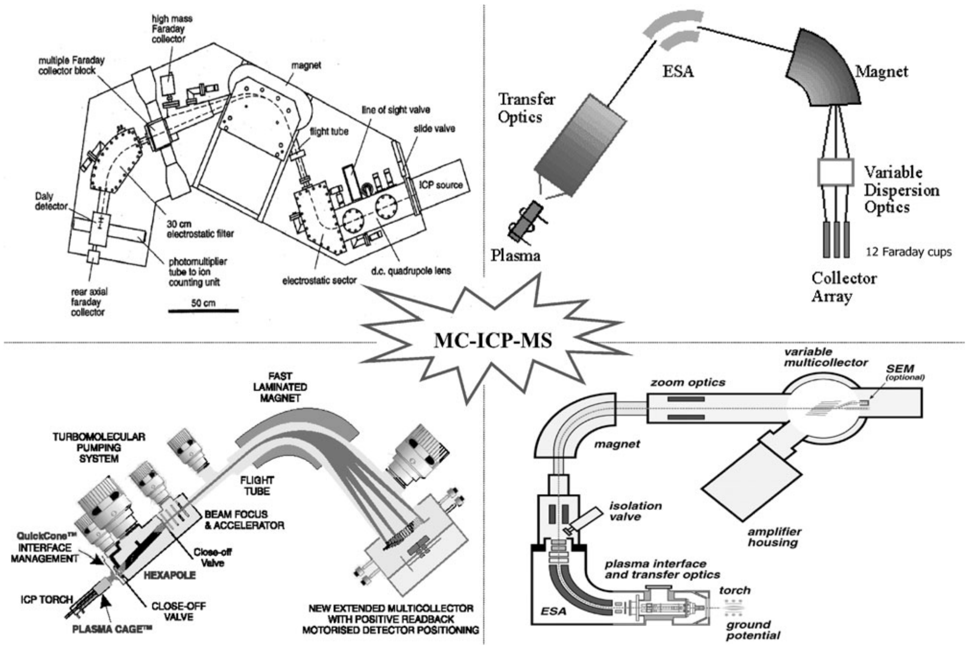


Fig. 3 MC-ICP-MS: Plasma 54 from VG Elemental, Nu Plasma from Nu instruments; Isoprobe from GV Instruments and Neptune from Thermo Electron ICP-MS (reproduced with permission of Nu Plasma, GV Instruments and Thermo Electron, with acknowledgment to mass spectrometer companies).

field mass spectrometers combining a magnetic and sector field with Nier Johnson geometry. In contrast, MC-ICP-MS Isoprobe (GV Instruments, former Micromass) only consists of a single magnetic sector field because an additional hexapole collision cell between the ICP ion source and magnet removes any possible disturbing interferences and reduces the kinetic energy spread of ions.

An interesting approach for the highest precise isotope ratio measurements in ICP-MS is represented by the Nu 1700 (the so-called "Big Mac") from Nu Instruments introduced and applied in Halliday's group at the Isotope Geochemistry Laboratory, ETH Zurich.[62] The experimental arrangement of this double-focusing mass spectrometer (see Fig. 4) with high dispersion and large geometry consists of a 750 mm radius, 70° magnet combined with a 943 mm radius 70° electrostatic analyzer (ESA). The high mass resolution ($m/\Delta m$, up to 10 000) of the MC-ICP-MS can be applied to solve a multitude of inherent interference problems of molecular ions with analyte ions of interest. The instrument possesses 16 Faraday collectors (10 fixed, 6 mechanically movable ones) and multiple ion counting with a high-abundance sensitivity filter. The main application fields of this most expensive MC-ICP-MS Nu 1700 are geoscience in order to study extremely small isotope variations in nature or geochronology for age dating of rocks.

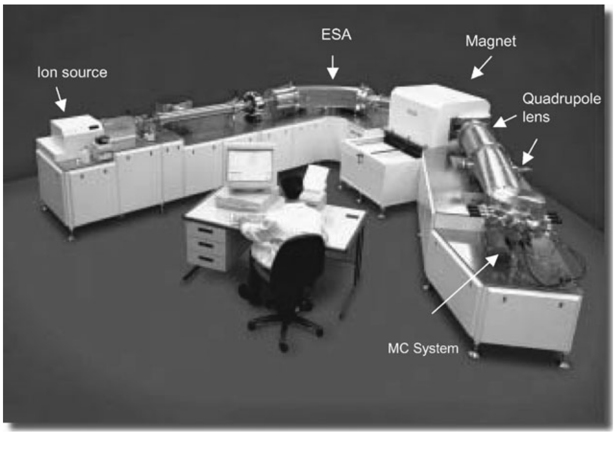


Fig. 4 Experimental arrangement of MC-ICP-MS Nu 1700 ("Big Mac") from Nu Instruments (reproduced with permission of Nu Instruments, with acknowledgement to J. G. Williams).

The Finnigan MAT 262, the VG ISOLAB-120 from former VG Isotopes, ISOPROBE-T from GV Instruments and the TRITON, Thermo Electron, are used as multicollector mass spectrometers for precise isotope ratio measurements with thermal surface ionization in TIMS. Due to the relatively low initial energy spread of the thermal ions (<1 eV), the Finnigan MAT 262 and the TRITION used single-focusing magnetic sector fields for the mass separation of ion beams and in addition a retarding potential quadrupole (RPQ) lens to increase the abundance sensitivity. The abundance sensitivity improvement by RPQ in TIMS (TRITON) is about a factor of 10 better in comparison to MC-ICP-MS (NEPTUNE) due to the smaller energy spread of the ions formed in thermal surface ionization.[48] The VG ISOLAB-120 mass spectrometer—designed for ^{9}Be/^{10}Be isotope ratio measurement—used an electrostatic analyzer prior to the entrance of an ion-counting detector to achieve high abundance sensitivity. The multicollector SIMS (NanoSIMS, ion microprobe from CAMECA) is available on the analytic market for precise isotope ratio measurements with a spatial resolution in the sub-μm range). The layout of MC-TIMS (TRITON) and the double-focusing NanoSIMS 50 with multiple ion collectors are shown in Fig. 5. The main application of NanoSIMS is in geological science. For example, Floss *et al.*[63] determined carbon and nitrogen isotope anomalies in anhydrous interplenary dust particles using NanoSIMS and found an association of a ^{13}C depletion with a ^{15}N enrichment.

Isotope ratio measurements on solid surfaces using secondary ions formed by the bombardment of sample surface with primary ions can be performed in the double-focusing SIMS (*e.g.*, from CAMECA) or TOF-SIMS (*e.g.*, from ION-TOF) instruments, as well. Both types of secondary ion mass spectrometers apply a single ion collector.

For isotope ratio measurements on solid samples by glow discharge mass spectrometry (GDMS) only single ion collector instruments are available (VG 9000 from VG Element). GDMS is mostly applied for trace element analysis and depth profiling and this mass spectrometric technique plays only a minor role in isotope ratio measurements. Several applications of GDMS and SIMS in isotope analysis are described by Betti.[31]

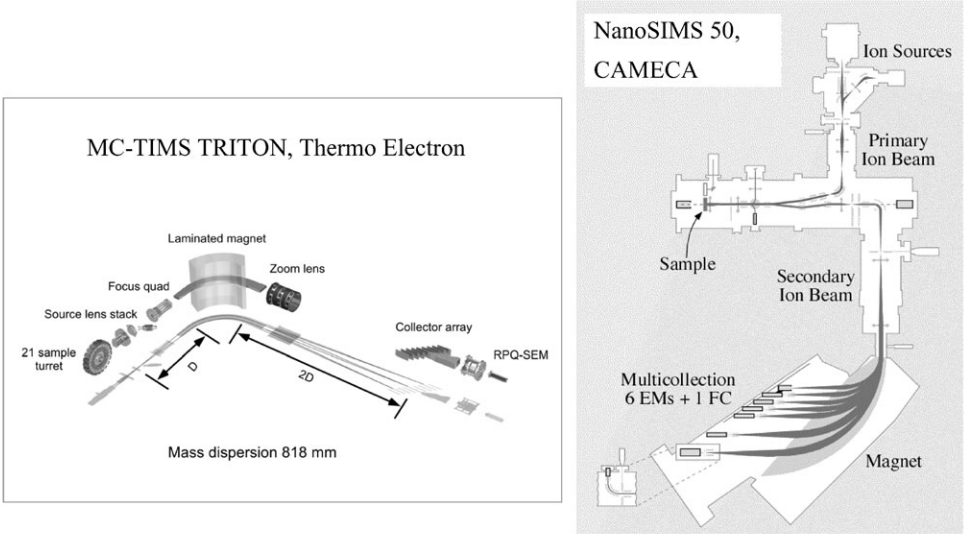


Fig. 5 MC-TIMS (TRITON, Thermo Electron, reprinted by permission of Elsevier Science Publisher, with full acknowledgment to M. E. Wieser and J. B. Schwieters[48]) and MC-SIMS (NanoSIMS 50, Cameca, reproduced with permission).

Measuring very low natural isotope abundances down to a level of 10^{-15} (*e.g.*, $^{41}Ca/^{40}Ca$, $^{60}Fe/^{56}Fe$) requires an ultra-sensitive method capable of handling a very large dynamic range of isotope analysis.[3] As the most powerful (sensitive and selective) mass spectrometric technique, AMS measures ion currents of abundant stable isotopes (*e.g.*, ^{12}C, ^{13}C) in Faraday cups and the rare radionuclides (*e.g.*, ^{14}C, $t_{1/2} = 5730$ a) are determined by ion counting in a solid state or gas detector. ^{14}C dating requires high-precision isotope ratio measurements in order to compete with existing beta-counting facilities.[3] Most AMS are equipped with a caesium sputter ion source (used in SIMS) for the formation of negative ions, which are accelerated with 20–75 kV in an "ion preparation stage" (consisting of, *e.g.*, an electrostatic analyzer and magnetic sector field). For the frequently required ^{14}C determination, the mass separated ion beam with $m/z = 14$ ($^{14}C^{-}$ $^{12}CH_2^{-}$ $^{13}CH^{-}$, but no $^{14}N^{-}$ ions are formed) is then accelerated and decelerated in a 3 MV Tandem Accelerator with a gas target or thin foil where disturbing isobaric molecular ions are dissociated and triple charged ions are generated. In a final analysis stage, for example, by a magnetic sector field, the interfering and dissociated ions are separated and the analyte ions $^{14}C^{3+}$ are ultrasensitively detected. Details on instrumental layouts and development of AMS are described by Kutschera.[3]

In RIMS,[34–37] one or more lasers are tuned precisely to the wavelength required for optical resonance excitation from the atomic ground state into the excited state up to the final ionization of evaporated atoms in order to get highly sensitive and selective ionization of analyte. Solid-state lasers on titanium—sapphire crystals have replaced the tunable dye laser systems—are coupled, for instance, to a time-of-flight mass spectrometer (TOF-MS) in RIMS as described by Wendt and Trautmann.[42] RIMS and AMS are monoelemental analytical techniques whereas ICP-MS, LA-ICP-MS GDMS and SIMS possess multielemental capability.

Limits for precision and accuracy of isotope ratio measurements and solving the problems

Several effects like instrumental mass bias, isobaric interferences, instrumental background, contamination on the solution introduction system, on the sampler and skimmer cone and lens system, mass scale drift effects, plasma instabilities, drifts of ion intensities and matrix effects limit isotope ratio measurements with respect to precision and accuracy of the analytical data.[2,64]

Detection limits and precision for isotope analysis are strongly dependent on the mass spectrometer used (quadrupole-based with and without collision cell, sector field with single ion collector or with multiple ion collectors), matrix composition and sample preparation steps (separation and enrichment factors).

The mass discrimination effect as a result of space charge effects plays an important role in mass spectrometry. For example, in ICP-MS a time-independent discrimination of ions with different mass occurs if the ions—formed in the inductively coupled plasma—leave the skimmer cone, whereby the Coulomb repulsion of positively charged ions results in a loss of transmission through the ion optical lens system. During ion extraction the light ions are deflected to a greater extent than the heavy ones, resulting in a measured isotope ratio of lighter to heavier isotopes which is smaller than the true value. Mass discrimination effects (mass bias)—depending on the experimental parameters used—decreases in ICP-MS with increasing atomic weight of the elements and are corrected by measuring the mass discrimination factor using a suitable isotope standard reference material as described in ref. 2 and 20. In TIMS the mass discrimination effect is a result of preferential evaporation of lighter isotopes. Whereas in ICP-MS the mass discrimination effect is time-independent, in TIMS time-dependent (but smaller) mass discrimination effects were observed.[65]

The dead time of the ion detector for counting rates higher than 10^6 cps is a further source of uncertainty in isotope ratio measurements in ICP-MS because mostly a lower number of counts are registered than actually occur. Dead time correction of the detector is required if extreme isotope ratios are measured by channel electron multipliers and pulsed counting systems.[66]

High isotope abundance sensitivity is desirable for the measurement of low-abundance isotopes in the presence of neighboring high-abundance isotopes.[56] The contribution of the neighboring peak to the intensity of a measured isotope—the abundance sensitivity—influences the accuracy of isotope abundance measurements.[67,68] For example, the determination of ^{90}Sr ultratraces in the presence of a high strontium concentration of natural isotope abundance is not possible at low abundance sensitivity of the mass spectrometer due to peak tailing of $^{88}Sr^{+}$ on the $m/z = 90$.[67] By the determination of ^{90}Sr an improvement of abundance sensitivity in sector field ICP-MS (ELEMENT) by changing of mass resolution from $m/\Delta m = 300$ up to 4400 from 2×10^{-5} to 9×10^{-7} was observed. Using helium as collision gas in quadrupole based ICP-MS the abundance sensitivity for $^{236}U/^{238}U$ determination was 6.3×10^{-8}.[56]

In addition, the occurrence of isobaric interferences of analyte ions with isobaric atomic or molecular ions can hamper the accuracy and precision of isotope ratio measurements. Isobaric interferences of atomic ions can be separated with a Fourier transform ion cyclotron resonance mass spectrometer (ICP-FT-ICR-MS).[69] However, this type of instrumentation is of less significance in isotope ratio measurements, because no commercial instrument is available to date.

Problems in ICP-MS due to the isobaric interferences of analyte ions and molecular ions can be solved by the application of double-focusing sector field ICP-MS at the required mass resolution, by the application of ICP-MS with a collision cell, or by the application of coupling (hyphenated) techniques such as ion chromatography, HPLC and CE with ICP-MS.[70–74] If the analyte occurs at extremely low concentrations matrix separation and enrichment of the analytes have been proposed for its analysis by several authors.[14,68,75,76] Trace/matrix separation, which is performed off-line or on-line, is used more and more frequently for isotope ratio measurements in order to avoid possible isobaric interferences, matrix effects and to reduce the detection limits.

High-precision isotope ratio measurements using multiple collector mass spectrometry

High-precision isotope ratio measurements are necessary for the study of fine isotope variation in nature, which is especially expected of light elements like Li, B, S and Si. Isotope variation has also been described for Ca, Fe, Cu, Sr, Nd, Hf, Os, Pb, U due to nuclear, physical or chemical processes.

Most applications of isotope ratio measurements by MC-ICP-MS therefore focus on the study of isotope variation in nature and on geological applications, especially in geochronology. The physical methods of geochronology (age dating of rocks) as an essential field in the earth sciences, which would not have been possible without mass spectrometry, are based on precise and accurate isotope ratio measurements, *i.e.*, age dating using the following radioactive decay: $^{87}Rb \rightarrow {}^{87}Sr$, $^{147}Sm \rightarrow {}^{143}Nd$, U/Th → Pb, $^{187}Re \rightarrow {}^{187}Os$, $^{176}Lu \rightarrow {}^{176}Hf$. Textbooks on isotope ratio measurements, including several applications in age dating by MC-ICP-MS, have been published by Platzner[1] and De Laeter.[77]

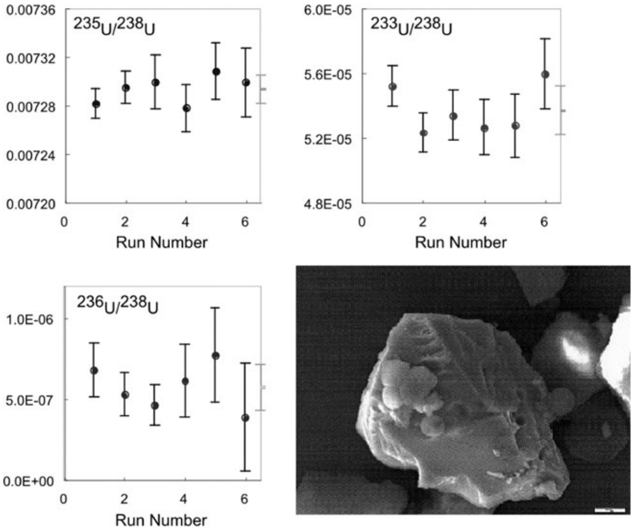


Fig. 6 Precision of uranium isotope ratios measured by MC-TIMS (TRITON) reproduced with permission, with full acknowledgment to J. B. Schwieters *et al.*[80]).

For example, accurate and reproducible U and Th isotope ratios for the geochronology of carbonates when analyzing small sample sizes (0.05–0.34 ng of Th measured by MC-ICP-MS in comparison to 0.3–1.4 ng Th for TIMS to obtain comparable precision) were presented by Seth *et al.*[78] Pietruska *et al.*,[79] who discussed an analytical technique for the determination of ^{226}Ra–^{230}Th–^{238}U disequilibria in volcanic rocks using MC-ICP-MS. MC-ICP-MS, which is much less time-consuming than TIMS, also yielded a better precision (2–3 times) for $^{232}Th/^{230}Th$ isotope ratios.

The results of uranium isotope ratio measurements by MC-TIMS (TRITON Thermo Electron) on a single uranium oxide reference particle (10 µm) measured by Schwieters *et al.*[80] are illustrated in Fig. 6. The high detection power of multiple ion counters in the MC-TIMS was used to study variation of uranium isotopes ^{233}U and ^{236}U in this micron size UO_2 particle.

The origin and migration of the Alpine Iceman was studied by Müller *et al.*[81] using MC-ICP-MS Nu 1700 by comparison of isotopic composition of radiogenic $^{206}Pb/^{204}Pb$ and $^{87}Sr/^{86}Sr$ in teeth, bones and soils. The authors determined the biological

Table 1 Application of stable isotope ratio measurements

Samples	Method	Stable isotopes	Precision	References
Human blood liver, muscle	MC-ICP-MS (NEPTUNE) separation by anion exchange chromatography	^{54}Fe, ^{56}Fe, ^{57}Fe	^{56}Fe—0.0049% ^{57}Fe—0.0071%	Walczyk and von Blanckenburg[20]
Environmental samples (soils, sediments, biological tissues)	MC-ICP-MS (NEPTUNE) (gold trap sample introduction)	^{199}Hg, ^{200}Hg, ^{201}Hg, ^{202}Hg	$^{199}Hg/^{202}Hg$, $^{201}Hg/^{202}Hg$ 0.0045–0.0105%	Xie *et al.*[84]
Single zircon grains	LA-MC-ICP-MS (NEPTUNE) diameter of laser crater: 20 µm	^{207}Pb, ^{206}Pb	$^{207}Pb/^{206}Pb$—0.22%	Bouman *et al.*[85]
Aquatic systems (MeHg) (isotope dilution analysis)	ICP-SFMS (ELEMENT) cold vapor technique	^{199}Hg, ^{200}Hg, ^{201}Hg, ^{202}Hg	$^{199}Hg/^{202}Hg$, $^{200}Hg/^{202}Hg$, $^{201}Hg/^{202}Hg$—0.6–1.4%; LOD: 0.2 ng L^{-1}	Stuerup *et al.*[23]
Organic solutions ($PbEt_4$ MeHgEt, $HgEt_2$)	GC-MC-ICP-MS (Axiom)	^{198}Hg, ^{199}Hg, ^{200}Hg, ^{201}Hg, ^{202}Hg, ^{204}Pb, ^{206}Pb, ^{207}Pb ^{208}Pb	$^{201}Hg/^{198}Hg$—0.077% $^{207}Pb/^{206}Hg$—0.5%	Krupp and Donard[86]
Soils (depth profiling)	ICP-SFMS (ELEMENT) separation by ion exchange	^{87}Sr, ^{86}Sr, ^{207}Pb, ^{206}Pb	$^{87}Sr/^{86}Sr$—0.08% $^{207}Pb/^{206}Pb$—0.07%	Prohaska *et al.*[87]
Silicates	MC-ICP-MS (NEPTUNE) separation by ion exchange	^{87}Sr, ^{86}Sr	$^{87}Sr/^{86}Sr$—0.0015%	Balcaen *et al.*[88]
CuS	MC-ICP-MS (Nu Plasma)	^{65}Cu, ^{63}Cu	$^{65}Cu/^{63}Cu$—0.01%	Ehrlich *et al.*[89]

age *via* $^{87}Sr/^{86}Sr$ isotope ratio measurements in various tissue, whereby variation from 0.717 to 0.719 was observed. The age of the Alpine Iceman, who lived 5200 years ago, was found to be 46 years.

The growth of Earth-like planets by mixing new material, volatile losses of accreted material to space and compositional change using several isotope systems like W, Sr and Pb was studied by Halliday.[82] Tl isotope variation on iron meteorites due to ^{205}Pb β-decay to ^{205}Tl was found by Rehkaemper and Halliday.[83] The results allow new conclusions to be drawn on the formation of elements in the solar system.

Selected applications of isotope analysis on stable isotopes are summarized in Table 1.

Determination of long-lived radionuclides by mass spectrometry

Advanced mass spectrometric techniques are advantageous, in particular, in long-lived radionuclide analysis at the ultratrace concentration level in contrast to radioanalytical techniques such as α-spectrometry (a main part of these radionuclides is an α-emitter), which have been dominant for many decades. The reason for increasing use of mass spectrometry methods is their high sensitivity, multielement capability, extremely low detection limits, short analysis time and high sample throughput. ICP-MS is at present the most frequently used mass spectrometric technique mainly applied for the fast analysis of radionuclide traces and ultratraces but also for isotope ratio measurements. In addition, ^{239}Pu and ^{240}Pu isotopes—relevant for the characterization of Pu originating in radioactive waste or environmental samples (as a result of nuclear fallout from nuclear weapons tests or nuclear power plants)—are difficult to analyze due to the very similar α energies of ^{239}Pu and ^{240}Pu (5.24 and 5.25 MeV, respectively). Therefore the radioanalytical techniques have been increasingly replaced by mass spectrometry in the last few years.

For example, $^{240}Pu/^{239}Pu$ isotope ratio measurements at ultratrace level can be reproduced to better than 3% with less than 120 fg of Pu by MC-ICP-MS using multiple ion counting as described by Taylor *et al.*[90]

Christensen *et al.*[91] identified the contamination sources of groundwater samples at the Hanford Site in Washington *via* high-precision uranium isotope ratio measurements by MC-ICP-MS (IsoProbe, GV Instruments). $^{240}Pu/^{239}Pu$ and $^{241}Pu/^{239}Pu$ isotope ratios were measured in Polish forest soils using double-focusing sector ICP-MS (Axiom MC-ICP-MS, using an electron multiplier as the single ion collector) by Ketterer *et al.*[92] The authors found unequivocal evidence of non-global $^{239+240}Pu$ fallout originating from the 1986 Chernobyl nuclear disaster. Two-component mixing between global nuclear fallout and fallout from the Chernobyl accident was observed by measuring plutonium isotopic composition in Polish soils.

In order to solve the interference problems of $^{238}Pu^+$ and $^{239}Pu^+$ with $^{238}U^+$ and $^{238}UH^+$, respectively, Tanner *et al.*[93] proposed an analytical ICP-MS technique with a band-pass reaction cell (ELAN DRC II) using carbon dioxide as the collision gas for an efficient reaction of U^+ and UH^+ (and non-reaction with Pu^+) in order to suppress disturbing interferences for plutonium and americium analysis. This technique allows the sub-ppt determination of ^{239}Pu, ^{240}Pu and ^{242}Pu (single ppt for ^{238}Pu) in the presence of an excess uranium matrix of 7 orders of magnitude without prior chemical separation.[93] With an analogous method using ELAN DRC II, Vais *et al.*[94] determined $^{238}Pu^+$ in urine (spiked with 10 $\mu g\ L^{-1}$ of uranium) with a detection limit of 0.245 $ng\ L^{-1}$.

The isotope analysis of plutonium (including $^{238}Pu^+$) was carried out by Guenther-Leopold *et al.*[95] by coupling high-performance liquid chromatography to the MC-ICP-MS (NEPTUNE, Thermo Electron, Bremen) using a flow injection device for solution introduction *via* measurement of transient signals.

Post-irradiation studies on nuclear fuel samples after the separation of analytes (to overcome interference problems of $^{238}U^+$ and $^{238}Pu^+$) by HPLC coupled to MC-ICP-MS (NEPTUNE) are described by the same group.[11] The isotopic composition (including ^{238}Pu) of two irradiated fuel samples with a similar burn-up level was determined with an external reproducibility between 0.04 and 0.2% and a precision in the ‰ range.

Kuczewski *et al.*[74] studied plutonium and neptunium species (oxidation state) in different humic-acid-containing groundwater samples by capillary electrophoresis (CE) at different pH values. Plutonium radionuclides were determined by ICP-MS in water samples,[28] soils and sediments,[92,96,97] urine,[98–100] plants,[13,101] food[102] and nuclear materials.[11,72,103] ICP-MS is increasingly being applied especially for the precise and accurate determination of $^{235}U/^{238}U$ isotope ratios at the trace and ultratrace level in medical samples (mostly in urine) to detect possible contamination with, for instance, depleted uranium.[18,51,52,104,105]

Perna *et al.*[73] described a sample cleanup procedure (using three analytical chromatographic columns to carry out the lanthanide/actinide speciation) for ^{241}Am determination in environmental samples (soils and sediment core samples from the Irish Sea) using ICP-QMS.

Izmer *et al.*[55] proposed a sensitive analytical technique for ^{129}I determination in contaminated soil and sediments by the online hot extraction of volatile analyte iodine in an oven (at 1000 °C with oxygen) coupled to ICP-CC-QMS (Platform). Oxygen was used as the extraction and collision gas and also for eliminating the isobaric interference of $^{129}Xe^+$, which disturbs ^{129}I detection. A cooling finger for the collection of iodine between the oven for hot extraction and ICP was introduced and achieved a significant improvement of the detection limit for ^{129}I in sediments (0.4 $pg\ g^{-1}$ *vs.* 30 $pg\ g^{-1}$ without cooling finger). $^{129}I/^{127}I$ isotope ratios of about 10^{-6} were measured in sediments at the ultratrace level with a precision of RSD $< 10\%$.[30]

The development of analytical methods using ICP-MS for the determination of long-lived radionuclides in samples of different matrix composition is focused on microanalytical techniques (in order to avoid possible contamination of instruments and to reduce the dose to the operator) thus improving the detection limits, the precision (relative standard deviation) and accuracy of mass spectrometry for isotope ratio measurements.[12,92,106,107] For example, nano-volume flow injection (FI, sample loop was about 50 nL) in ICP-SFMS for the isotope analysis of uranium and plutonium at the ultratrace concentration level with an absolute detection limit, *e.g.*, for plutonium, of 0.015 fg ($\sim$38 000 ^{242}Pu atoms) has been developed in our laboratory.[106] The precision of $^{235}U/^{238}U$ measurements *via* transient signals in FI-ICP-SFMS was in the low % range.

Nowadays, the analysis of radionuclides with shorter half-lives, such as ^{90}Sr ($T_{1/2} = 29.1$ a), ^{241}Am ($T_{1/2} = 241$ a) and ^{226}Ra ($T_{1/2} = 1600$ a), can also be carried out with low detection limits.[13,67]

Fine uranium isotope variations of $^{234}U/^{238}U$ (enrichment by factor 1.5 compared to the IUPAC table value of the isotopic composition of elements[109])—due to α decay of ^{238}U *via* ^{234}Th and ^{234}Pa in ^{234}U—in the Sea of Galilee and the Sahina spring were found by ICP-SFMS and MC-ICP-MS as well.[2]

Pu isotope analysis at ultratrace level after separation on TEVA resin and enrichment of Pu from 100 L lake water for the Sea of Galilee was performed by MC-ICP-MS (Nu Instruments).[28] Studies of the separation procedure for 2.1 pg ^{242}Pu spiked to 100 L of lake water result in a yield of 62%. The detection limit for Pu measurement by MC-ICP-MS was 3×10^{-20} $g\ mL^{-1}$. ^{239}Pu was detected in 100 L lake water at a concentration level of about 3.6×10^{-19} $g\ mL^{-1}$. The measured $^{240}Pu/^{239}Pu$ isotope ratio by MC-ICP-MS of 0.17 is

Table 2 Application of isotope ratio measurements for radionuclide analysis

Samples	Method	Radionuclides	Detection limits/ isotope ratio	References
Fission product solution	ETV-ICP-MS	^{79}Se	13 ng L^{-1}	Compte *et al.*[108]
Nuclear fuel samples	MC-ICP-MS (Neptune) HPLC (on-line)	^{238}Pu, ^{239}Pu, ^{240}Pu, ^{241}Pu	^{238}Pu/^{239}Pu $\sim$ 0.067 ^{240}Pu/^{239}Pu $\sim$ 0.56	Guenther-Leopold *et al.*[95]
Soils	ICP-SFMS (VG Axiom) after separation	^{239}Pu, ^{240}Pu, ^{241}Pu	^{240}Pu/^{239}Pu $\sim$ 0.18–0.35 ^{241}Pu/^{239}Pu $\sim$ 0.003–0.004	Ketterer *et al.*[92]
Soils and sediments	ICP-SFMS (ELEMENT)	^{239}Pu, ^{240}Pu	^{240}Pu/^{239}Pu $\sim$ 0.18–0.2	Nygren *et al.*[97]
Sediments	ICP-CC-MS (Platform) hot extraction	^{129}I	0.4 pg g^{-1} ^{129}I/^{127}I $\sim$ 5 $\times$ 10^{-7}	Izmer *et al.*[30]
Soils (Chernobyl)	LA-ICP-SFMS (ELEMENT) (LINA-Spark)	^{239}Pu, ^{240}Pu	0.25 pg g^{-1} ^{240}Pu/^{239}Pu = 0.4	Boulyga *et al.*[96]
Moss, plant, soil, sediment	ICP-SFMS (VG Axiom) after separation	^{239}Pu, ^{240}Pu,	^{240}Pu/^{239}Pu $\sim$ 0.19–0.26	Agarande *et al.*[101]
Food	ICP-SFMS +USN (ELEMENT), ion extraction	Pu	0.03 pg g^{-1}	Evans *et al.*[102]
Lake and river water	ICP-SFMS (ELEMENT) MC-ICP-MS (NuPlasma) after separation	^{239}Pu, ^{240}Pu (in 100 L sea water)	$\approx$0.1 fg L^{-1} (ELEMENT) $\approx$0.01 fg L^{-1} (NuPlasma) ^{240}Pu/^{239}Pu $\sim$ 0.17	Becker *et al.*[28]
Urine	ICP-SFMS (ELEMENT) ICP-CC-MS (Platform)	^{90}Sr	0.4 pg L^{-1} (ELEMENT) 2 ng L^{-1} (Platform)	Vonderheide *et al.*[67]
Urine	ICP-SFMS (ELEMENT) after separation (1 L urine)	^{239}Pu, ^{240}Pu	1 $\times$ 10^{-18} g mL^{-1} ^{240}Pu/^{239}Pu $\sim$ 0.14 (synth. sample)	Zoriy *et al.*[98]

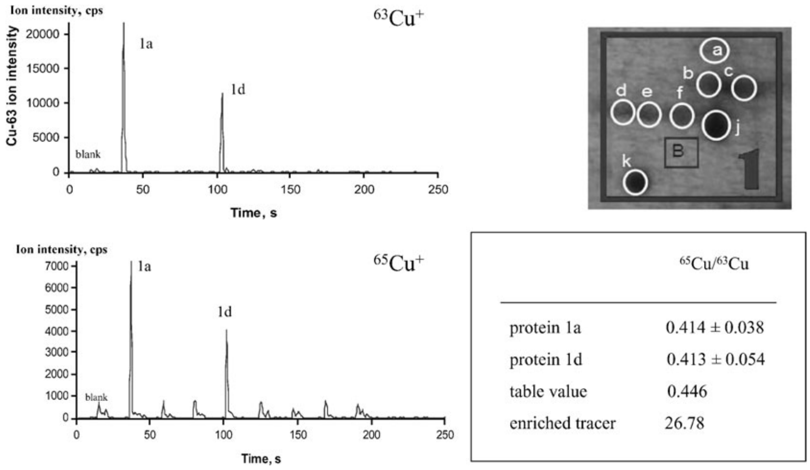
evidence for plutonium contamination as a result of global nuclear fallout after nuclear weapons tests in the sixties.

Several applications for the determination of long lived radionuclides are summarized in a recent review[12] and Table 2.

Isotope ratio measurements by laser ablation inductively coupled plasma mass spectrometry

ICP-MS coupled with a laser ablation system (LA) to create LA-ICP-MS opens up the possibility of direct isotope analysis on solid samples, mostly without additional sample preparation steps. Today LA-ICP-MS is used as a sensitive mass spectrometric technique for the direct sample introduction of solid samples in ICP-MS in order to determine the content of ultratraces.[110,111] This powerful analytical technique uses the evaporation of sample material by a focused laser beam (mostly using a Nd-YAG laser with $\lambda/4 = 266$ nm) in an inert gas atmosphere (*e.g.*, Ar) under normal pressure and the postionization of evaporated and ablated material in an inductively coupled plasma of the ion source of an ICP-MS. Commercial laser ablation systems (*e.g.*, LSX-200 or LSX-500, CETAC, USA and LUV 266, Merchantek, UP 213 or UP 266, New Wave, USA) are coupled to quadrupole analyzers or sector field ICP-MS with single or multiple ion collectors.

Seltzer[112] used LA-ICP-MS for screening soils to detect depleted uranium as an anthropogenic contaminant by a quadrupole-based instrument (PQ ExCell, Thermo Elemental, Franklin, MA) coupled to a UP 266 laser ablation system (New Wave/Merchantek, Fremont, CA). An ultrasonic nebulizer with desolvator was used to generate a thallium-containing aerosol for an independent internal standardization to consider



	^{65}Cu/^{63}Cu
protein 1a	0.414 ± 0.038
protein 1d	0.413 ± 0.054
table value	0.446
enriched tracer	26.78

Fig. 7 Transient signals of ^{63}Cu and ^{65}Cu in protein spots of Alzheimer's brain samples measured by LA-ICP-MS (isotopic-enriched ^{65}Cu spike solution was doped to the gel after 2D gel electrophoresis).[21] Reprinted by permission of Elsevier Science.

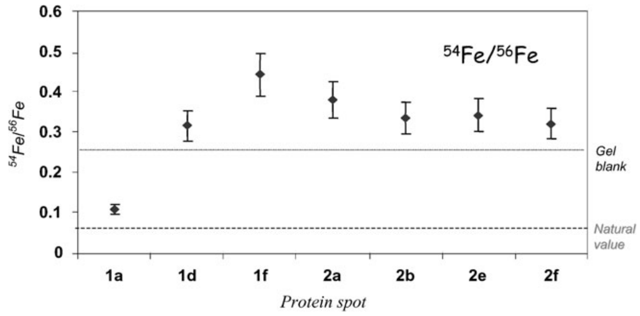


Fig. 8 ^{54}Fe/^{56}Fe isotope ratios in selected protein spots of Alzheimer's brain samples measured by LA-ICP- MS (isotopic-enriched ^{54}Fe spike solution was doped to the gel after 2D gel electrophoresis).[21] Reprinted by permission of Elsevier Science.

the mass discrimination effect by isotope ratio measurements of uranium and possible plasma instabilities, mass scale drift effects *etc*. Differentiation between depleted uranium and naturally occurring uranium was accomplished on the basis of uranium isotope analysis. ^{235}U/^{238}U isotope ratios measured for field samples were in good agreement with those derived from gamma spectrometry measurements.

For determining plutonium radionuclides in soils and sediments, Boulyga *et al.*[96] proposed direct analysis by LA-ICP-MS (using a high ablation rate LINA-Spark Atomizer coupled to a double focusing sector field ICP-MS). To minimize uranium hydride formation and peak tailing of ^{238}U$^+$ on m/z = 239, the measurements were performed at a mass medium resolution of LA-ICP-MS. An isotope ratio of ^{240}Pu/^{239}Pu ~0.4 was measured in contaminated Chernobyl soil samples, the detection limit for Pu was determined as 0.3 pg g^{-1}and the isotope dilution technique was applied for concentration analysis.

Recent developments in LA-ICP-MS at our laboratory focus on the application of LA-ICP-MS in protein research in order to identify metal-containing protein spots.[113] Proteins separated by two-dimensional gel electrophoresis were fast-

Table 3 Selected application in isotope ratio measurements by LA-ICP-MS

Sample	ICP-MS	Laser system/ wavelength	Measured isotope ratio	RSD (%)	Application	Reference
Mantle sulfides	MC-ICP-MS Nu Plasma	Merchantek LUV/ 266 nm	^{187}Os/^{188}Os	0.05–1	Geochronology	Pearson *et al.*[115]
			^{187}Re/^{188}Os			
NIST glass SRM minerals	ICP-QMS X-7	Surelite I Continuum/ 266 nm	^{206}Pb/^{207}Pb	0.2–0.4	Geology	Crowe *et al.*[116]
			^{208}Pb/^{207}Pb	0.3–0.4		
Pb buttons	ICP-CC-QMS Elan 6100	GeoLas ArF/193 nm	^{106}Pd/^{108}Pd	2.0	Geology	Vanhaecke *et al.*[117]
			^{195}Pt/^{194}Pt	2.9		
Molybdenite	ICP-SFMS ELEMENT	UV laser probe/ 266 nm	(^{187}Re + ^{187}Os)/ ^{185}Re	0.2	Geochronology	Malinovsky *et al.*[118]
Zircon	ICP-SFMS ELEMENT	Brilliant Quantel/266 and 213 nm	^{206}Pb/^{238}U	0.099–0.021	Geochronology	Tiepolo[119]
			^{207}Pb/^{206}Pb	0.65–1.98		
			^{208}Pb/^{232}Th	0.41–18.3		
Glasses	MC-ICP-MS Axiom	LSX 200 266 nm	^{11}B/^{10}B	0.1	Geology	Roux *et al.*[120]
Human bones	ICP-SFMS ELEMENT	Ablascope/213 nm	^{87}Sr/^{86}Sr	0.1–0.2	Biology and life science	Prohaska *et al.*[121]
Flower leaves	ICP-SFMS ELEMENT	Ablascope/213 nm (cooled LA ablation chamber)	^{235}U/^{238}U	0.4–1.3	Biology and life science	Zoriy *et al.*[114]
			^{234}U/^{238}U	1.6–2.0		
			^{236}U/^{238}U	1.0–2.1		
NIST SRM 611, Zircon, opal	MC-ICP-MS Plasma 54	LSX 100 213 nm	^{234}U/^{238}U	0.02–0.04	Geochronology	Stirling *et al.*[122]
			^{230}Th/^{238}U	0.05		
Separated protein spots in 2D gels	ICP-SFMS ELEMENT	Ablascope/213 nm (cooled LA chamber)	^{67}Zn/^{64}Zn	5	Metallomics (tracer experiments)	Becker *et al.*[21]
			^{65}Cu/^{63}Cu	5		
			^{54}Fe/^{56}Fe	5		
Geological and biological samples	MC-ICP-MS Axiom	LSX 200 and NewWave LUV 266 nm/213 nm	^{87}Sr/^{86}Sr	0.002–0.09	Geochronology	Waight *et al.*[123]
			^{84}Sr/^{86}Sr	0.01–0.8		
Geological and environmental samples	ICP-SFMS ELEMENT	LINA-Spark/ 1064 nm	^{37}Cl/^{35}Cl	3	Environmental, geology	Boulyga and Heumann[124]
			^{81}Br/^{79}Br	3		
			^{129}I/^{127}I	3		
Geological glasses	ICP-SFMS ELEMENT	New Wave UP/ 213 nm	^{208}Pb/^{206}Pb	0.1–0.2	Earth science, geochemical research	Jochum *et al.*[125]
			^{207}Pb/^{206}Pb	0.1–0.2		
NIST Cu SRM 976 NIST Fe SRM 665	MC-ICP-MS Nu Plasma 500	GeoLas 200CQ/ 193 nm	^{65}Cu/^{63}Cu	0.04	Fundamental	Hirata *et al.*[126]
			^{56}Fe/^{54}Fe	0.05		

screened by microlocal analysis using LA-ICP-MS with respect to metals. In order to study the formation of proteins containing Cu, Zn and Fe in human brain samples tracer experiments using isotope-enriched ^{54}Fe, ^{65}Cu and ^{64}Zn spikes were carried out on 2D gels proteins of Alzheimer's disease brain proteins.[21] The protein spots were screened systematically by LA-ICP-MS with respect to ^{54}Fe/^{56}Fe, ^{65}Cu/^{63}Cu and ^{64}Zn/^{67}Zn isotope ratios in metal-containing proteins. The isotope ratio measurements using LA-ICP-MS indicate certain protein spots with natural isotope composition of the three transition metals investigated. Fig. 7 shows transient signals of ^{63}Cu and ^{65}Cu in protein spots of Alzheimer's disease brain samples measured by LA-ICP-MS after tracer experiments with isotope-enriched ^{65}Cu spike solution on 2D gel. Cu^+ ion intensities were observed for both Cu isotopes with remarkable ion intensities from 8 investigated protein spots of Section 1 of 2D gel in protein spots 1a and 1d. However, ^{65}Cu/^{63}Cu isotope ratio measurements yielded natural isotope abundances. This means that both these proteins already contained the metal investigated in the original proteins and are stable enough to survive reducing conditions during gel electrophoresis. Furthermore, proteins with changed ^{54}Fe/^{56}Fe and ^{64}Zn/^{67}Zn isotope ratios were detected, which demonstrated an accumulation of tracers within the protein complexes during the tracer experiments (see Fig. 8 for Fe-containing proteins). MALDI-FTICR-MS was employed for the identification of single protein spots from Alzheimer-diseased brain.[21] An improvement of LA-ICP-MS for isotope ratio measurements on biological samples with respect to precision and accuracy was observed with a cooled laser ablation chamber compared to the non-cooled chamber as proposed in the author's lab.[114]

Selected applications of LA-ICP-MS in the isotope analysis of biological, geological and environmental samples are summarized in Table 3.

Isotope dilution mass spectrometry

An excellent possibility of obtaining accurate quantitative date (element concentrations) in atomic spectrometry is the application of isotope dilution analysis (IDA), which requires reliable isotope ratio measurements. Fundamentals and their application are reviewed by Heumann.[127] Isotope dilution mass spectrometry (IDMS) was recognized as a primary measurement method, by means of which accurate results with sufficiently small uncertainties can be achieved.[128] An important advantage of IDMS in comparison to other quantification strategies is that analyte recovery does not have to be quantitative, providing that isotopic equilibrium has been achieved between all of the analyte and the added spike material.[129] For application in the isotope dilution technique and for tracer experiments using isotope-enriched spikes, Merck (Darmstadt, Germany) launched the production of new sets of isotopically enriched materials such as ^{53}Cr- or ^{111}Cd-enriched spike calibration solutions which were characterized by the Institute for Reference Materials and Measurements (IRMM, Geel, Belgium).[129,130] The isotope dilution technique is employed in species analysis in biological systems,[22] *e.g.*, for the determination of mercury species in tuna material,[23,131] or in aquatic systems.[23] Further applications of the isotope dilution technique are the determination of selenomethionine in human blood serum by capillary HPLC-ICP(ORC)MS[132] or sulfur speciation in gas oil, diesel or heating fuel by LA-ICP-MS.[133]

Regelous *et al.*[134] reported on the use of the isotope dilution technique (using ^{233}Pa spike with a half-life of 26.97 days) for the quantitative measurement of 20 fg of protactinium in silicate rocks after chemical separation of the actinide from rock matrix by MC-ICP-MS (Neptune, Thermo Electron, Bremen—equipped with nine Faraday detectors, one secondary electron multiplier and a retarding potential quadrupole for high abundance sensitivity measurements). ^{231}Pa/^{233}Pa isotope ratios were measured with a precision of 0.5%, the detection limit was 200 ag mL^{-1}. ^{226}Ra concentration ranges from 0.36–0.42 fmol kg^{-1} were determined by MC-ICP-MS (Nu Instruments) in the Ross Sea *via* the isotope dilution technique.[135]

Boulyga and Heumann[24] proposed an analytical method for the direct determination of halogens (Cl, Br and I) in powdered geological and environmental samples using isotope dilution laser ablation ICP-MS. The detection limits of LA-ICP-IDMS are in the low and sub-µg g^{-1} range for halogens.

7. Conclusions

Of the atomic mass spectrometric techniques, ICP-MS and LA-ICP-MS are currently dominant due to the possibility of sensitive isotope ratio measurements of elements in the pg g^{-1} to fg g^{-1} range in water, geological, biological and environmental samples. ICP-MS is also an excellent tool for the analysis of aqueous solutions, especially with on-line coupling techniques (ETV, HPLC, GC, ion chromatography, flow injection) for performing isotope analysis at the ultratrace level. The significance of ICP-MS in precise isotope ratio measurements at ultratrace levels is increasing, especially when multicollector and/or double-focusing sector field instruments are used.

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