Atomic spectrometry update. Clinical and biological materials, foods and beverages

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This update is a little shorter than in recent years, reflecting the fewer original papers published. However, the trend for a large number of review articles has continued and these cover a wide range of important topics. In the 2012 update, a noticeable increase in work involving very small samples was evident. These observations continue through into the current review. This was particularly seen with sample introduction systems used for ICP-MS. A microflow device for aerosol generation, based on thermal inkjet technology, provided for analysis of highly dissolved solids at a flow rate of 1 μL min^{-1} while other high performance arrangements were described which operated at slightly larger delivery rates. As in previous years, major topics include investigations of the metabolism of As and Se. We have also previously reported on the techniques to measure Pt–DNA adducts, developed in the last few years. It is encouraging to see that these are now being applied to studies of platinum anti-cancer treatments in cell cultures and in patients. There are some interesting new methodologies. Quantum dots appeared for the first time in this review with an indirect assay for measuring very low concentrations of protein in urine. A protein conjugate formed with CdTe quantum dots was isolated and the Cd measured by ICP-MS. XRF has poor sensitivity for low atomic number elements but in another indirect assay, Li in mineral water was determined by forming a potassium lithium periodatoferrate complex and measuring the Fe. Magnetic particles are used in some immunoassays to effect separation of reagents and a similar approach was developed using Fe_3O_4 magnetite nanoparticles modified with 1-(*p*-acetyl)phenyl)-3-(*o*-ethoxyphenyl)triazene to extract and preconcentrate Hg from water and fish samples. Concern over the amount of As in fish and rice and the potential for this element to appear in other food products is evident from studies involving fish oils and organic brown rice syrup. Anyone tempted to eat alligator meat can be reassured that concentrations of Cd, and Pb are very low. We are pleased to have a new contributor to this review; Sarah Hill has considerable experience with ICP-MS techniques including the use of this technique for imaging.

1 Reviews

This latest update adds to that from last year[1] and complements other *reviews of instrumental techniques* in the series of Atomic Spectrometry Updates from the last year.[2–6] Two reviews, with different authors but featuring the same department in Santa Maria, Brazil, discussed how analysis of biological samples using ICP-MS has developed during the last 10–15 years. One concentrated primarily on sample preparation strategies, such as extraction and solubilisation, derivatisation, pre-concentration, appropriate for analyte separation and speciation.[7] The second was directed at techniques applied to speciation of vapour forming elements, LC-, GC-, CE-ICP-MS.[8]

Other reviews dealing with *sample preparation* focussed on micro-extraction procedures, reinforcing the observations made in our recent ASUs about the growing interest in this approach to the analysis of foods[9] and other biological specimens.[10,11]

Although discussed in more detail in a separate ASU,[6] *speciation* is particularly important for biological samples. Relevant reviews from this last year include a presentation from the 4th IUPAC Symposium on Trace Elements in Food[12] in which Lobinski and his colleagues related analytical developments to food regulations and quality control of production. Opportunities for expansion of this type of work provided by ES-HR-ICP-MS were also mentioned. The more specific topics of CRMs for Hg speciation,[13] Hg speciation in seafood[14] and I in environmental and biological materials[15] were also reviewed. Ibanez-Palomino *et al.*[13] listed the characteristics of an ideal biological CRM for Hg in terms of matrix, species present and their concentrations and compared these against the CRMs used in recent research papers. Clemens *et al.*[14] in a very specialised review looked at species-specific and species-unspecific ID-analysis as used to demonstrate and correct for inter-species transformations of Hg during sample preparation. Determination and speciation of I in clinical samples has not previously received much attention but Mereda-Pineiro *et al.*[15] have now comprehensively reviewed work with this biologically important element discussing sample pre-treatment, techniques for measurement, approaches to speciation and the role of I in the environment and in humans.

Exposure to undue levels of Cd is now uncommon in many countries but still has considerable economic importance in some parts of the world. Thus, Wu *et al.*[16] described new work since 2006 (224 references) in terms of analysis, speciation, imaging within cells and toxicity of Cd-containing quantum dots.

From the work discussed in Section 5.2, it is evident that the interest in showing the distribution of elements within tissues and cells is increasing. An extensive review of tissue analysis by imaging MS was prepared by Oppenheimer and Drexler.[17]

2 Metrology, interlaboratory studies, reference ranges

The rationale for determination of *measurement uncertainty*, together with validation of an analytical method, so as to give high quality data which may be assessed with respect to statutory limits, reference limits and data from other studies, was presented by Bocca *et al.*[18] In applying their principles to the validation of analytical procedures to measure 20 elements in human blood, these workers reported linearity, LODs, bias on CRMs, repeatability, reproducibility and expanded uncertainty. In keeping with this philosophy, Jitaru *et al.*[19] measured six elements in tomato paste by HR-ICP-MS, presenting the method validation data including the measurement uncertainty.

In previous ASUs, we have referred to work for *in vivo* measurement of Pb in bone using XRF and have highlighted various analytical and calibration problems associated with what is still a developing technique. Bellis *et al.*[20] from the New York State Department of Health initiated an *interlaboratory comparison study* using tibia from their Pb-dosed goats. Nine samples were distributed with concentrations of 1.8–35.8 μg g^{-1} dw (measured by ICP-MS). The mean reported values were in the range 4–55.3 μg g^{-1} bone mineral. Results from eight of the participants showed no significant bias while the remaining seven had from 1 to 6 biased results. The study confirms the

need for further work before *in vivo* XRF can be regarded as a reliable technique for bone Pb measurement.

The national metrological institutes of Japan and the USA (NMIJ and NIST) independently report development and *certification of CRMs* for trace elements in dried tea leaves and a green tea extract, respectively.[21,22] The NIST also presented work on the identification and quantification of selenoproteins (selenoprotein P, glutathione peroxidase 3 and selenoalbumin) in a candidate human plasma SRM.[23]

Ethical considerations associated with collecting blood samples from children mean that there are limited reliable *reference ranges* for many parameters, including trace elements. This was exemplified by Zeager *et al.*[24] who obtained the ranges reported from 10 different laboratories for Al in plasma, serum or urine. These varied considerably and the authors concluded that further work in association with the CDC Biomonitoring Project should be considered. However, Lin *et al.*[25] were given approval to take blood samples from 2115 healthy children in the USA, aged 0.5–18 years and measured concentrations of Cu and Zn in the serum. There were no differences associated with gender or fasting status. The reference interval for Zn was 64 to 124 μg dL^{-1} while for Cu the age related ranges were: 75–153 for those less than 10.3 years, 64–153 for those aged 10.3 to 12.5 years and 57–129 for those older than 12.5 years (concentrations in μg dL^{-1}). These Cu values are inconsistent with those from other workers who found much lower concentrations in infants, with adult levels (76–160 μg dL^{-1}) being attained by about one year of age and no change thereafter. The decrease beyond 10 years of age has not previously been reported. For an Italian biomonitoring programme, the concentrations of 20 elements were measured in blood from 252 subjects aged 13–15 years, using HR-ICP-MS.[26] As part of a project to assess release of Ti from bone fixation implants, a method was established to determine concentrations of the metal in serum using HR-ICP-MS and samples from 40 control subjects were analysed.[27] The mean value was 0.26 μg L^{-1}. Further work established that more than 99.8% of the Ti was bound to transferrin. Within the context of a cognitive function and ageing study, House *et al.*[28] measured Al, Cu and Fe in four regions of brains from 60 aged subjects. The sample preparation and analysis included extensive precautions to reduce contamination which was monitored by regular inclusion of blank samples. The dry weight concentrations, in μg g^{-1}, were: not detected (ND) to 33, ND to 384 and 112–8305 for Al, Cu and Fe, respectively. Median values were 1.02, 17.41 and 286.16 μg g^{-1}, respectively.

3 Sample collection and preparation

3.1 Collection and storage

Developments in recent years that have increased the sensitivity for analyses mean that potential contamination during *sample collection, storage and analysis* has become even more important. Hodnett *et al.*[29] collected blood from 10 volunteers using stainless steel needles, "butterfly" winged infusion needles and plastic cannulae. The samples were then analysed for Co, Cr, Mn and Ni by ICP-MS. While there was no significant differences in concentrations associated with the different devices some unexpectedly increased results were obtained. It was recommended that stainless steel needles may be used but that a repeat specimen is collected using a plastic cannula if an aberrant result is obtained. In addition to the collection procedure, the specimen tube may also be responsible for producing erroneous results. Contamination of the sample is well recognised but Malavolta *et al.*[30] demonstrated that EDTA used as the anticoagulant will give erroneous results in investigations of elemental speciation in plasma. By contrast, lithium-heparin anticoagulant was acceptable.

In some previous ASUs, we mentioned work in which *real-time measurements* were made in blood that was pumped from a vein through to the analytical system. This approach has been further developed as seen in the report by Su and colleagues.[31] In their recent work, saline-perfused rat brain extracellular fluid was taken to a microdialysis unit with a polycarbonate membrane where it was mixed with maleic acid, through 80 cm × 0.018 cm i.d. PTFE tubing which acted as a solid phase extraction to remove the salt matrix and enrich the analyte concentrations for determination by ICP-MS. The analytes were detached from the PFTE tubing with 0.5% HNO_3. After establishing the perfusion in anaesthetised rats, concentrations of Cu, Mn, Ni and Zn were monitored following intra-peritoneal administration of a dose of $MnSO_4$. The concentration of Mn increased in the brain's extracellular fluid but there were no changes involving the other ions.

3.2 Digestion, extraction and preconcentration

In an elaborate investigation to optimise conditions for *microwave-assisted digestion* of fish samples, Low *et al.*[32] varied microwave power, time, heating ramp rate, digestion temperature and addition of H_2O_2 or HCl. Of these, the radiation time, ramp and temperature were the most important but the best settings were element specific. It was reported that the most useful compromised conditions were to ramp to 185 °C in 10.5 min, hold for 14.5 min, with 1600 W microwave power. The reagents used were 2.5 mL HNO_3, 0.5 mL HCl and 7 mL H_2O. The recommended conditions for microwave digestion of flour were reported by Ren *et al.*[33] Polgari *et al.*[34] compared 'normal-volume' microwave digestion, digestion using micro vessels and vapour-phase digestion. The normal-volume approach afforded better destruction of organic matrix and dilution of inorganic residue but higher LODs compared with the other procedures due to the greater dilution factors. For this reason, it is preferred for quantification by XRF because of reduced background and self-absorption of the fluorescent radiation.

Ultrasound-assisted extraction continues to be used with tissues and food samples. In a novel arrangement, Zhang *et al.*[35] achieved 40% increase in the extraction of organic Hg species from seafood samples when a combination of ultrasonic bath and ultrasonic probe was used. Inorganic and total Hg were completely extracted within 60 s as shown by analysis of CRMs.

Reviews of work involving *microextraction procedures* were cited in Section 1. New work reported in the last year included the measurement of Hg in human saliva by AFS. This involved complexation of the Hg^{2+} from 25 mL saliva with DDC followed

by extraction into fine droplets of 1-undecanol which were cooled to solidify into a microdrop.[36] An enrichment factor of 182 was reported, giving an LOD of 2.5 ng L^{-1}. Variations around this general approach were used to determine the concentrations of As in blood and urine by HG-AAS[37] with LODs of 5 ng L^{-1} and 0.02–10 μg L^{-1}, respectively, and Se species in garlic by ETAAS[38] for which the LOD was 15 ng L^{-1}.

Reports of new procedures for more conventional *pre-concentration* were also seen during the last year. Rofouei *et al.*[39] added Fe_3O_4 magnetite nanoparticles modified with 1-(*p*-acetylphenyl)-3-(*o*-ethoxyphenyl)triazene to samples to effect adsorption of Hg^{2+}. The particles were recovered by application of a magnetic field and the Hg^{2+} eluted for measurement by ICP-AES. The technique was used for analysis of water and fish samples providing analyte enhancement of up to 500-fold. A glass microcolumn packed with thioureidopropyl functionalized silica gel was used by Kovachev *et al.*[40] to enhance the concentration of Pd from serum and urine 90-fold. Methodological parameters, flow rate *etc.* were optimised and elution from the column was facilitated by microwave irradiation. Digests of food samples, with the pH adjusted to more than 7, were applied to a chelating column containing InertSep ME-1 and the Cd eluted with 0.2 M HNO_3.[41] This procedure achieved a modest increase in concentration but more usefully it removed Mo, Sn and Zr which caused a spectral interference within the measurement of Cd by ID-ICP-MS.

4 Progress with analytical techniques

4.1 Progress with analytical techniques: mass spectrometry

4.1.1 Inductively coupled plasma-mass spectrometry. Often, biological sample analysis is restricted by quantity or volume. Recent studies used *microflow nebulisers* to overcome this. A new aerosol generation system, based on thermal inkjet technology, termed 'drop-on-demand' (DOD) was reported by von Niessen *et al.*[42] The technique enabled the use of ultra-low flow rates (1 μL min^{-1}) for samples with high dissolved solids, such as urine and serum, to be analysed without causing clogging/blockages which is commonly observed with other microflow nebuliser systems. Calibration was achieved using a dosing frequency-based technique and could be applied for external calibration or standard addition in the case of complex matrices. Lariviere *et al.*[43] described the use of a high matrix interface system for the measurement of Be in autopsy tissues. After optimisation, the instrumental LOD was 0.6 ng L^{-1} despite the high level of salt present in digests from samples such as bone or hair. The theme of small volumes was echoed by Takasaki *et al.*[44] who reported the development of a micro-volume sample introduction system for ICP-MS. The system comprised of a 20 μL injection loop with a high-performance concentric nebuliser and heated cyclonic spray chamber, giving a flow rate of 10 μL min^{-1} and good signal stability. Validation using NIST SRM 1577b gave results in good agreement with certified values and, with other analytes, demonstrated the applicability to clinical micro-volume samples. Bentlin *et al.*[45] also described the use of FI for the analysis of lanthanide elements in red wine after ultrasonic digestion for origin discriminatory purposes. Micro-volumes of sample (50 μL) were used in combination with a PFA micro-nebuliser and aerosol desolvation.

The inclusion of *on-line sample preparation to small volume analysis* was applied by Su *et al.*[31] for the *in vivo* analysis of rat brain extracellular fluid. Micro-dialysis was used to extract the samples whilst SPE was used to preconcentrate and remove salt from the matrix. Excellent LODs and CRM recoveries were obtained for the system, offering a valuable insight into *in vivo* metal interaction in brain extracellular fluid. Direct online analysis was also demonstrated by Leufroy *et al.*[46] to investigate the bioavailability of As in seafood samples. The method showed benefits over batch processes due to the constant removal of the leached species.

The *optimisation of collision/reaction cell ICP-MS* for the measurement of As, Co, Cr, Fe, Ni, Se and V in food products was reported by Kadar and colleagues.[47] An experimental design approach was applied to determine the optimum conditions for best analytical performance *versus* interference removal. In another work, Richardson *et al.*[48] described Mn analysis in whole blood and plasma without the use collision cell technology. This was achieved using a new design of skimmer cone which successfully removed the FeH interference that could not be achieved with collision cell mode. The methodology was validated by external quality assurance samples. Balaram *et al.*[49] discussed using ^{129}Xe, naturally present as a contaminant in Ar, as an internal standard for the analysis of water. It was validated using NIST SRMs and typically achieved <5% RSD. It offered an alternative internal standardisation approach to minimise off-line sample preparation or sample dilution when mixed online.

A review article by Khouzam *et al.*[12] summarised the current position of *analytical techniques and methods required for state of the art speciation in food products*. The application of speciation analysis in the food industry is growing, particularly with legislation drivers, *e.g.*, Cr^{III} and Cr^{VI}. The review also discussed the wider availability of ESI-MS^n which has enabled significant advances in this research field. Preud'homme *et al.*[50] applied SEC-ICP-MS with ESI-MS^n for the identification of selenium metabolites from the conversion of selenite into organic compounds and the enrichment of selenium in yeast.

The combination of *dual analysis by ICP-MS and other organic-based MS* continues to provide structural data with elemental identification for a variety of applications. Easter *et al.*[51] reported the use of SEC-ICP-MS and LC-MALDI-TOF/TOF for the investigation of selenium interaction with protein markers related to cerebral vasospasm in stroke patients. Although the work was preliminary, the proof of concept was demonstrated along with the need for further research. The elucidation of the metabolic pathway for a gold-containing drug using LC-ICP-MS and LC-ESI-MS was described by Albert *el al.*[52] In a similar approach, Meermann *et al.*[53] reported the use of HPLC-ICP-MS combined with ID analysis and ESI-MS to determine the metabolites of a bromine-containing anti-tuberculosis drug. The use of faeces offered an *in vivo* measurement approach that avoided the use of ^{14}C radiolabels in clinical studies.

In what is possibly a unique piece of work, Tang *et al.*[54] developed an assay for the *indirect determination of total urinary*

protein. Bio-conjugates were formed between proteins and a CdTe quantum dots label. The Cd signal measured by ICP-MS was shown to be directly proportional to the concentration of protein, providing an extraordinarily sensitive assay. The LOD for human urine was 0.008 μg mL^{-1}.

Calibration strategies for analysis of single hair strands by LA-ICP-MS were investigated by Kumtabtim *et al.*[55] Using either powdered hair CRM or human hair doped with known amounts of analytes, mounted on sticky tape, very similar calibration curves were produced. The $^{34}S^{+}$ ion was used as the internal standard.

4.1.2 Other mass spectrometry techniques. The use of other MS techniques for biological analysis has shown development. Li *et al.*[56] reported the measurement of *U isotope ratios in human tissue samples* of occupationally exposed to U using TIMS. In a unique but unusual approach, Almstrand and colleagues[57] analysed exhaled particles by TOF-SIMS as an indirect method of determining the composition of respiratory tract lining fluid. Since this acted as a bio-marker for respiratory diseases it was possible to successfully discriminate control individuals and asthma patients using partial least squares analysis.

A *comprehensive study of arsenic biochemistry* was described by de Bettencourt *et al.*[58] using HPLC-ESI-MS^n and ESI-FTICR-MS. The results provided evidence for the metabolic pathways of As, of which little was previously known.

4.2 Atomic absorption spectrometry

Electrothermal AAS was promoted as a useful technique for determination of phosphorus in fish diets and faeces.[59] The optimum heating programme, using 1 mg mL^{-1} La as the chemical modifier, was developed and afforded an LOD of 0.15 mg g^{-1} with 100 mg dried sample. This method was said to be simpler, faster and required a small sample compared with the usual colorimetric procedures. Concentrations of Al were measured in wheat flour by ETAAS using a high resolution continuum source analytical system.[33]

The recent development of *high resolution molecular absorption spectrometry*, with ETV to generate the molecular species, was mentioned in our 2011 ASU.[1] Now, the technique has been applied to the analysis of blood and foods. Aramendia *et al.*[60] measured the concentration of Al in blood as AlF. A modifier with 5% $NH_4F{\cdot}HF$ promoted the formation of AlF and also improved the destruction of the sample matrix such that aqueous calibration, rather than standard additions, was possible. This method, which had an LOD of 1.8 μg L^{-1} was used to demonstrate a positive correlation between Al concentrations in blood and water in a limited number of cases of death by drowning. Concentrations of F in tea were measured as the CaF molecule by Welz and his colleagues.[61] The LOD was 0.16 mg L^{-1} and the linear range extended to 25 mg L^{-1}.

4.3 Atomic emission spectrometry and laser induced breakdown spectroscopy

There has been very little by way of *innovation in the area of atomic emission* during the last year. A procedure involving ETV-ICP-AES was used by Mukhtar and Limbeck[62] to measure the concentrations of Ba, Co, Cu, Mn, Ni and Pb in synthetic gastric juice following extraction from airborne particulates. The increased sensitivity compared with conventional ICP-AES was used to show that bioaccessibility of these elements varied from 32 ± 14% (Ni) to 97 ± 36% (Pb). With a dual nebulisation system, Benzo *et al.*[63] were able to simultaneously measure hydride forming and non-hydride forming elements by ICP-AES. Results for 16 elements were in good agreement with the certified values for four different biological CRMs. Gilon *et al.*[64] compared LA-ICP-AES and LIBS with conventional acid digestion and ICP-AES, for the determination of Ca, Mg, Na and Zn in milk powder. The laser ablation results were biased by up to 60% due to a powerful matrix effect.

4.4 Atomic fluorescence spectrometry and vapour generation procedures

It was impossible to discern any really novel development or application relating to *vapour generation techniques* in the last year. Simultaneous measurement of hydride forming and non-hydride forming elements was mentioned in the previous section. Mercury species in red wine were measured by GC-ICP-MS after derivatisation with 1% m/v $NaBPh_4$ and the sum of values compared with total Hg concentrations determined by FI-CV-ICP-MS.[65] However, when real samples of wine from Argentina, Brazil, Chile and Uruguay were analysed, the Hg species were below the LODs with total Hg being no more than 0.55 μg L^{-1}.

4.5 X-ray fluorescence

4.5.1 *In vivo* XRF. The last year would appear to have been a quiescent period with respect to *in vivo XRF*. A new instrument was developed by Fleming *et al.*[66] with a silicon PiN diode detector and a miniature X-ray tube to excite L-line fluorescence. This was tested by measuring Pb in plaster of Paris bone phantoms. Models with varying amounts of added Pb were used as the bare plaster or coated with either 1.2 or 2.7 mm resin layers to simulate soft tissue. The LODs obtained with these samples were 7.4, 17 and 43 μg g^{-1}, respectively. The sensitivity, therefore, is insufficient for the equipment to have real application given that the typical concentrations of Pb in bone found in other studies are less than 10 μg g^{-1}. An inter-laboratory study for Pb in bone measurements was discussed in Section 2. In a new application of *in vivo* XRF, Moise *et al.*[67] measured Sr concentrations in finger and ankle bone (cortical and trabecular bone, respectively) in an osteoporotic subject prior to and then at intervals after commencing oral treatment with a daily dose of 680 mg Sr as strontium citrate. Baseline concentrations were 0.38 and 0.39 μg g^{-1} and increased without reaching a plateau. After 800 days, the concentrations were 7 and 15 times greater than at the pre-treatment time. The K-alpha X-ray peak at 14.16 keV was used for these measurements.

4.5.2 Quantitative analysis. Developments where XRF and related techniques were used for elemental imaging in tissues

are discussed in Section 5.2. While not exactly *in vivo* analyses, investigations of ancient *bone* are not dissimilar to the work required to validate and characterize the methodologies described in the previous section. Human lumbar vertebrae samples dating from the 10th Century AD were analysed by Janos *et al.*[68] using EDXRF. Bones from two sites in Hungary were examined to measure concentrations of 12 elements. Considerable post-mortem exchange between the soil and the skeletal remains was evident for many of the elements but concentrations of Br, Sr and Zn were thought to be consistent with lifetime levels. Even older, fossil bones were examined, also by EDXRF, by Thomas and Chinsamy.[69] Noting the poorer precision and larger bias associated with hand held devices, they considered inter-sample trends in the EDXRF spectra rather than measuring concentrations. Readings for elements such as Ca, Fe and Sr were attributed to groundwater percolation and it was suggested that the procedure employed may assist with defining the original location of museum specimens. Bones from living subjects, albeit collected at surgery, were examined by micro-PIXE and PIGE to investigate the distribution and concentration of essential elements at the boundary between bone and cartilage.[70]

Gherase and Fleming[71] developed a method to *calibrate XRF measurements in nail clippings*. Nail phantoms were prepared to contain 0–20 μg g^{-1} of As and Se. Clippings of 20, 40, 60, 80 and 100 mg were taken and X-ray emission spectra produced with a portable X-ray tube. The XRF signal in a number of counts *versus* elemental concentration was used to prepare calibration lines for similar analysis of human nail clippings.

Zawisza and Sitko developed a strategy to determine Li in mineral waters by XRF despite the poor fluorescence and long wavelength associated with such a light element.[72] The method involved forming a stoichiometric precipitate of a potassium lithium periodatoferrate complex, re-dissolving and pipetting onto Mylar foil for measurement of the Fe. The absolute LOD for Li by this indirect approach was 1 μg. A report of a preferred procedure to prepare biological samples prior to the determination of *elements with low* A_r, by TXRF[34] was included in Section 3.2.

An equally simple method to measure concentrations of Gd in urine and plasma by TXRF, in samples from patients given Gd-based MRI contrast agents was reported by Telgmann *et al.*[73] The LODs were 100 and 80 μg L^{-1}, respectively and the method allows circulating levels and excretion to be monitored for up to 20 h post administration. Official catalogues of licensed medicines, such as the British Pharmacopoeia, include specifications relating to maximum allowable limits of possible contaminants including metals. Antosz *et al.*[74] published a report that compared TXRF with other analytical techniques for the determination of residual metals in active pharmaceutical ingredients. These workers refer to the small sample size, short analysis time and minimal matrix interferences associated with TXRF, and also noted equivalent performance from instruments with molybdenum or tungsten excitation sources. Other interesting but straightforward *applications of XRF* to the analysis of biological materials are included in Sections 5.3, 5.4, 6 and 7 and in the Tables.

5 Applications: Clinical and biological materials

Table 1 gives a summary of the work reviewed during this period.

5.1 Metallomics

Developments in *metallomics and speciation is extensively reviewed in a separate Update* appearing in the August issues of JAAS.[6] This section is intended to give an indication of the range of work relevant to clinical, biological interests, foods and beverages from the last year.

Platinum-containing drugs are very effective in the treatment of certain types of cancer but their use is complicated by unpleasant side effects and by the development of resistance in some patients. Resistance appears to be linked to the formation of Pt–DNA adducts. Studies of the *biochemistry of Pt* in the cell cytoplasm and nucleus can provide clues as to the mechanisms of action of these drugs in individual subjects. To this end, the work of Sharp and his colleagues is particularly relevant. Methods were developed using HPLC with ES-MS and SF-ICP-MS which allowed the identification of bi-functional Pt–diaminocyclohexane adducts involving oxaliplatin and mono- and di-nucleotides with adenine and guanine, formed *in vitro.*[75] Quantification of intra-strand DNA adducts with oxaliplatin in cultured colorectal cells was also undertaken by SF-ICP-MS.[75] In further work with both cultured tumour cell lines and leucocytes from patients treated with Pt-drugs, the distribution of Pt within the cytoplasm and nucleus was determined.[76]

The complexity of *metabolism* of Se continues to become more evident. With ultra performance-LC (UPLC), ICP-MS and ES-linear-trap, Preud'homme *et al.*[50] identified 49 compounds involved in the metabolism of Se^{IV} in yeast. These included selenoorganic amino acids and oligopeptides at very low concentrations and some previously reported structures were re-interpreted on the basis of high resolution mass spectra and mass accuracy associated with these techniques. In preparation for an investigation of the metabolism of a Br-containing anti-tuberculosis drug, Meermann *et al.*[53] established a procedure to separate Br species by HPLC-ICP-MS with on-line ID. Structural information for the species was developed by ES-MS. Gold-containing drugs have long been used in the treatment of rheumatoid arthritis but their mode of action remains unknown. Interactions with thiol compounds have previously been suggested to be involved in the metabolism of these compounds and Albert *et al.*[52] worked with auranofin to determine the nature of its binding to glutathione and albumin. The data obtained using LC-ICP-MS and LC-ES-MS indicated exchange mechanisms resulting in loss of the –SH group from the parent drug and covalent bonding of the complementary triethylphosphine Au^{I} structure. Subsequent oxidation of the phosphine ligand to form phosphine oxide may then take place.

Polyacrylamide gel electrophoresis is a regularly used procedure for the *separation of proteins* within biological samples. To identify and quantitate metalloproteins from among the large number of other proteins element specific

techniques may be used. Becker *et al.*[77] separated extracted protein from slugs by PAGE and, using LA-ICP-MS observed three bands, corresponding to 75, 100 and 150 kDa, with considerable Zn contents. Despite further work using MALDI-TOF-MS and various databases, they failed to identify these Zn-proteins. It is not often that plant proteins feature in this ASU and it is even more unusual to consider Cd in plants. However, Polatajko *et al.*[78] worked with a Cd-binding protein in Cd exposed spinach plants. Following extraction and separation by PAGE, a Cd-protein was located by LA-ICP-MS. From further investigation by nano-ESI-FT ion cyclotron resonance MS, this was identified as ribulose-1,5-biphosphate carboxylase/oxygenase, an enzyme normally activated by Mg^{2+}. Kutscher *et al.*[79] proposed to measure the concentration of ovalbumin by adding *p*-mercuribenzoic acid as a label and determining the Hg by nanosecond LA-ICP-MS following PAGE. Quantification was achieved by label-specific ID analysis with ^{199}Hg-enriched label.

As in previous years, several procedures for *speciation* were reported. Most were extensions to, or variations around, established methods. Reference to these is shown in the Tables while two of note are mentioned here. A novel material, nickel–aluminium layered double hydroxide, provided a nano-sorbent for the speciation of Cr and Mn in drinking water.[80] The Cr^{VI} and Mn^{VII} oxyanions at pH 6.0 adsorbed onto, or exchanged with NO_3^- within the sorbent interlayer. There was no retention of Cr^{III} and Mn^{II}. In an unusual application, Matsukawa *et al.*[81] simultaneously measured concentrations of D- and L-SeMet enantiomers in mouse plasma. The methodology required purification of the SeMet by cation exchange chromatography, addition of HCl to give the methyl ester followed by *N*-acylation with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride. Separation and measurement were achieved by GC-MS with selected-ion monitoring. The method was developed to allow studies of the pharmacokinetics of the SeMet enantiomers.

5.2 Applications for clinical and biological materials: imaging with MS and X-rays

The field of imaging using solid sampling techniques for the analysis of biological materials has continued to grow. Three review articles have succinctly summarised the application of *bio-imaging using advanced techniques*.[17,82,83] There remains to be a strong focus on mass spectrometric based instrumentation, with several publications reporting the development of new technologies to aid imaging studies. A new LA chamber was designed by Fricker *et al.*[84] for ICP-MS which offered improved washout times (within 2.6 s for 99.9% of the signal), high spatial resolution on large samples (dimensions up to 230 mm × 34 mm × 16 mm, $L \times W \times D$) and increased throughput for small sized samples. Becker and colleagues[85,86] have considered the issue of handling large quantities of data which can be generated during LA-ICP-MS analysis. A new software tool[85] was developed to simplify the task of manipulating raw data, whilst the use of k-means cluster analysis[86] provided a method of grouping specific tissue features and/or element profiles to compare across several tissue slices from an individual or a set of individuals. Both of these tools offer ways to reduce the time spent on data handling and to aid the identification of regions of interest.

Calibration is an important consideration for *quantitative solid sampling* analysis due to the strong matrix effect. It was reported[87] that homogenised rat brain, spiked with aqueous elemental standards and encapsulated in a sol–gel matrix generated by tetraethyl orthosilicate, created matrix-matched biological standards which were homogenous and stable at room temperature for at least three months. Matusch *et al.*[88] demonstrated that meaningful quantitative analysis of human mesencephalon slices stored in formalin for over 10 years was possible by LA-ICP-MS for Fe, Mn and Pb using matrix-matched standards.

The imaging of tissues can offer valuable insight into *metabolic pathways and disease states*. Moreno-Gordaliza *et al.*[89] reported the use of LA-ICP-MS to map kidney tissue slices in rats dosed with cisplatin to investigate Pt accumulation and nephrotoxicity. A novel use of iodine as a marker for single cells and cell nuclei was demonstrated in fibroblast cells and liver tissue slices.[90] The authors further extended the method to apply I as an internal standard for LA-ICP-MS to correct for tissue thickness inhomogeneity when using lanthanide-based antibody labels for the detection of breast cancer markers. The feasibility of using enriched Zn isotopes as bio-tracers was demonstrated by Urgast *et al.*[91] using LA in combination with MC-ICP-MS to create Zn isotope ratio images of rat brain tissue slices to investigate Zn kinetics at the microscale.

Protein identification using gel electrophoresis for *protein separation in combination with LA-ICP-MS* for element specific detection received significant attention. Kutscher *et al.*[79] described the quantification of ovalbumin labelled with *p*-hydroxy-mercuribenzoic acid by external calibration using protein standards and with ID analysis with a ^{199}Hg enriched label, the latter offering superior accuracy and precision. Two groups focussed on the identification of plant proteins. Wu *et al.*[92] reported the application of 2D-PAGE to investigate the mechanisms of Cu tolerance in the roots of *Elsholtzia splendens.* Using LA-ICP-MS as a detector, the spots of metal-containing proteins were located, digested with trypsin and analysed by LC-MS-MS for structural elucidation. In a similar approach, Polatajko *et al.*[78] used native anodal PAGE and electroblotting onto membranes to screen for Cd-containing proteins by LA-ICP-MS in *Spinacia oleracea L.* after exposure to Cd. Relevant bands of interest were trypsin-digested and analysed by nano-ESI-FTICR for structural identification. Additionally, the authors applied SEC-UV-ICP-MS to study metal-bound complexes in the trypsin digests, making a very thorough investigation.[78]

X-ray fluorescence offers a non-destructive alternative for bio-imaging applications. This was demonstrated by the use of SR-XRF to quantify and to determine the distribution of a Gd-based MRI contrast agent in mouse liver samples.[93] It was tested with hepatitis infected tissues and displayed a reduced uptake of the Gd agent when compared to controls, offering a prospective new diagnostic test for this drug but also potentially useful for pharmacological studies using exogenous elements. Malinouski *et al.*[94] employed SR-XRF microscopy to Se imaging in mouse liver and kidney tissues, leading to the discovery of localised pools of Se present as glutathione peroxidase 3. The use of XRFM was also applied by Lagomarsino *et al.*[95] to investigate

Mg imaging in whole cells in combination with atomic force microscopy. This allowed correction of uneven sample thickness to produce concentration maps of intracellular Mg.

Two other works of note relate to *less common imaging techniques*. Pineda-Vargas *et al.*[96] applied micro-PIXE and micro-RBS to fingernails to build 3D quantitative elemental distributions of major, minor and trace elements. The second publication[97] reported the use of TEM and SIMS to investigate the migration of Sm in the mammary gland of lactating Sm-dosed rats. The combination of the techniques enabled the determination of Sm levels and distribution within the cells.

5.3 Multielement applications

5.3.1 Biological fluids. Several interesting reports, apart from determinations of reference ranges, were noted. Most were concerned with relatively *unusual sample types*. Release of Cr and Ni from orthodontic appliances into saliva was assessed by Amini *et al.*[98] using ETAAS. Samples collected from 28 subjects with orthodontic appliances had mean concentrations of 2.6 and 18.5 ng mL^{-1} for Cr and Ni, respectively, while in samples from same gender siblings without appliances concentrations were 2.2 and 11.9 ng mL^{-1}. The Ni, but not Cr, results were significantly higher for the test group. Kruger *et al.*[99] provided a comprehensive description of a method to analyse human follicular fluid using SF-ICP-MS. The procedure was used to determine the concentrations of 24 elements in samples from 64 women undergoing *in vitro* fertilisation treatment. Analyses of human bronchial lavage samples, in the context of occupational exposure, have been cited in our recent ASUs. Suzuki *et al.*[100] obtained similar samples from calves with mycoplasma bronchopneumonia infection and used PIXE to determine 18 elements. Compared with samples from healthy animals, there were increased concentrations of Br, Ca, Fe, K, P and Zn, and also a higher Zn : Cu ratio which was proposed as a diagnostic test.

Given that there is rarely a problem collecting sufficient volume of *urine* for analysis, the work of Kumtabtim *et al.*[101] may appear somewhat bizarre. Single droplets of urine, dried onto a suitable support, were analysed by LA-ICP-MS. The concentrations of 18 elements were determined with LODs of 0.003–0.58 μg g^{-1}. The authors suggested that the procedure might be applicable to forensic investigations when only a small amount of dried urine was available.

Malavolta and colleagues[30] developed a rapid procedure for speciation of Cu, Fe, Se and Zn in *serum* using a monolithic anion exchange microcolumn for HPLC-ICP-MS. Differences in speciation results were seen with RMs from different sources. In an unprecedented undertaking, 64 elements were determined in 140 serum samples by ICP-MS from patients with gouty arthritis, and controls.[102] The measured concentrations were then used to develop a 12-element profile said to be unique to this condition. This profile was subsequently tested with a further 39 patients and 13 healthy controls and claimed to have a sensitivity of 1.00 and a specificity of 1.00, for prediction of gout. Such perfection is almost unheard of in medical diagnostics.

5.3.2 Tissues, hair and nails. Font *et al.*[103] determined Pb and Sr isotope ratios in human head and facial *hair* to assess whether these parameters relate to geographical location. It was observed that changes in ratios rapidly reflected movements of the subjects between areas with different isotopic composition.

To assess whether formalin stored *brain* tissue may be used with frozen samples, in order to investigate rare neurological disorders, Matusch *et al.*[88] prepared quantitative elemental maps from brain slices stored for more than 10 years in buffered formalin. Compared with a fresh sample, the distribution of Cu and Zn within the substantia nigra had been lost but meaningful assessments of Fe, Mn and Pb were possible with the formalin fixed samples. As discussed in Section 4.1, Becker and colleagues continue to investigate quantitative elemental mapping in tissues, especially in brain. Instead of their usual LA-ICP-MS procedure, they have also employed laser microdissection to isolate small areas of tissue (0.014 to 0.338 mg) from mouse brain haematoma. The samples were digested and analysed by ICP-MS using a micronebuliser-desolvation system and it was found that concentrations of Fe, Na and Zn were 2 to 10 times higher than in normal tissue. The normal concentrations of Al, Cu and Fe in aged brains were noted in Section 2.

As pointed out by Thomas and Chinsamy,[69] *bone chemistry* provides important information which may be of cultural as well as physiological interest. However, very little novel work was reported in the last year. Using handheld devices to generate EDXRF spectra from fossil bone and tooth specimens, and principal components analysis of the data, these authors noted distinct differences in concentrations of Ca, Fe and Sr in samples from two locations in South Africa. Bone and cartilage was examined by Kaaber *et al.*[70] in healthy and osteoarthritic samples. Proton induced gamma-ray emission and micro-PIXE were used to derive data on low A_r ($z < 15$) and heavier elements, respectively. Normal cartilage contained significant amounts of Na and S while Zn concentrations were high at the bone cartilage interface.

5.4 Progress for individual elements

5.4.1 Aluminium. It was something of a surprise to read that drowning is still a difficult autopsy diagnosis. Researchers continue to seek new analytical methods to aid diagnosis and approaches have included the determination of trace elements in blood as markers for drowning diagnosis. Aramendia *et al.*[60] described *a novel method for the determination of Al in whole blood and water* for exactly this purpose. Aluminium was quantitatively determined by measurement of the molecular absorption of AlF using HR-CS-ETA- molecular absorption spectrometry. The AlF diatomic molecule was generated in the furnace by reaction with $NH_4F{\cdot}HF$, which also improved removal of the blood matrix for samples collected in EDTA or heparin anticoagulant. Calibration was performed with aqueous standards and an LOD of 1.8 μg L^{-1} was reported. The authors claimed that measurement of molecular absorption as opposed to more conventional AA overcame most of the interferences experienced with the latter technique. The method was used to determine Al in blood and drowning-water samples from eight suspect cases of drowning and observed a significant positive correlation between Al in drowning-water and blood,

Table 1 Clinical and biological materials (for column 3, L = liquid, S = solid, Sl = slurry)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
Al	Blood, water	—; —; —	In an investigation of Al as a potential marker for drowning, a procedure was developed to quantify Al by means of HR-CS molecular absorption spectrometry, by measuring the molecular absorption of AlF, formed *in situ* by addition of $NH_4F \cdot HF$, with an LOD of 1.8 μg L^{-1}. Calibration was obtained with aqueous standards, since $NH_4F \cdot HF$ also promoted matrix removal	60
Al	Erythropoietin	AA; ETA; SEC	Al present as a contaminant in erythropoietin formulations was shown to be bound mainly to this protein, even in the presence of human serum albumin, citrate or phosphate	104
Al	Brain	AA; ETA; L	Al, Cu and Fe concentrations were measured in the temporal, frontal, occipital and parietal lobes of 60 brains donated to the Cognitive Function and Ageing Study, after microwave aided acid digestion. The median content was 1.02 μg g^{-1} dw (Al), 17.41 μg g^{-1} dw (Cu) and 286.16 μg g^{-1} dw (Fe)	28
Al	Serum, plasma, urine	AA; -; -; MS; ICP; L	A survey of paediatric reference ranges applied in clinical laboratories indicated wide variation	24
As	Nails	XRF; —; —	A strategy for the calibration of a portable XRF instrument using phantom nail clippings of increasing mass was reported	71
As	Chinese medicines	MS; ICP; L	Morphological and microscopic characteristics of four Chinese medicines containing As (orpiment, containing As_2S_3, realgar, containing As_4S_4, arsenolite and arsenic trioxide, As_2O_3) were proposed as a simpler and less costly method for their authentication. The identity of arsenolite and arsenic trioxide was confirmed by ICP-MS analysis	159
As	Urine, groundwater, foodstuffs	AA; HG; FI	To assess the risk of human exposure to As in areas of West Bengal (India), samples of groundwater, locally grown foodstuffs and urine were collected and analysed. The intake of As from foodstuffs was estimated as 560 μg per day for adults and 393 μg per day for children. The level of total As in urine ranged between 154 and 276 μg L^{-1}	107
As	Urine	MS; ICP; HG/HPLC	In a longitudinal study of the exposure to As in rural Bangladesh, the urinary As concentrations in 5 years old children (median: 51 μg L^{-1}, 5^{th}–95^{th} percentiles: 16–355 μg L^{-1}) were significantly correlated with those measured at 1.5 years old and to maternal levels during gestation	108
As	Blood, urine	AA; HG; FI	The speciation of As^{III} and As^{V} was achieved by applying DLLME to blood (5 mL) or urine (15 mL) samples. As^{III} was complexed with APDC at pH 4, followed by extraction and back extraction in HCl prior to analysis. Total As was determined after reduction of As^{V} to As^{III} with KI and ascorbic acid. As^{V} was determined by subtraction. An LOD of 5 ng L^{-1} was reported and an RSD of <5%	37
As	Urine	MS; ICP; HPLC	^{72}Ge was used as a pseudo-isotope for As in order to apply "ID type" analysis to the screening of As species in urine. On spiked samples, recovery ranged from 90% to 115% and the RSD was <10%. A comparison with the method of standard additions was carried out	160
As	Urine	MS; ICP; HPLC	iAs, MMA and DMA contributed to 75% of the total As concentrations measured in urine from 153 residents in Latium (Italy), chronically exposed to iAs *via* water and food. Dimethylthioarsinic acid was found in 33% of the samples at concentrations up to 6 μg As L^{-1}	109
As	Faeces, microorganisms suspensions	MS; ICP; HPLC	As part of an investigation of As metabolism by microorganisms from the human gut, five As species (As^{III}, As^{V}, DMA^{V}, MMA^{V} and monomethylmonothioarsenate) were separated and quantified by HPLC-ICP-MS, using a Hamilton PRP-X100 anion exchange column. Two more species (MMA^{III} and DMA^{III}) were determined using a Zorbax C_{18} column	110
Au	Glutathione, human serum albumin	MS; ICP; LC	The metabolism of Auranofin, a Au^{I}-based drug, was explored by LC-ESI-MS and LC-ICP-MS	52

Table 1 (*Contd.*)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
B	Drinking water, urine	AE; ICP; L	In an area with high levels of naturally occurring B, the level of B in public tap water ranged from 0.22 to 11.3 mg L^{-1} and in bottled water from 0.01 to 12.2 mg L^{-1}, compared with the WHO guideline value of 2.4 mg L^{-1}. The B levels in urine of residents was between 0.45 and 17.4 mg L^{-1} (median: 4.28 mg L^{-1}) and was correlated ($r = 0.64$) with the corresponding levels in tap water sampled from their homes	113
Be	Tissues	MS; ICP; L	With the aid of a high matrix interface, the determination of Be in acid digested tissues by means of ICP-MS was achieved with an instrumental LOD of 0.6 ng L^{-1}	43
Bi	Water, hair	AA; F; L	Hair samples, washed with acetone and triply distilled water, were digested with HNO_3–$HClO_4$, followed by 30% H_2O_2 and 1 M H_2SO_4, then dissolved in water to a volume of 50 mL. An aliquot of 10 mL of water or hair digest was subjected to DLLME using 5-Br-PADAP as the complexing agent, acetone and dichlorobenzene. Phases were separated by centrifugation and the bottom phase diluted with EtOH prior to analysis. An enrichment factor of 28.6 was reported. The LOD was 3.0 ng mL^{-1} and the RSD was 1.5%	111
Bi	Serum	AE; ICP; L	An enrichment factor of 81 was achieved by cloud point extraction of Bi^{3+} with 8-hydroxyquinoline and Triton X-114. An LOD of 0.12 μg L^{-1} was obtained. The RSD was 2.3% and recovery was between 92.3% and 94.7%	112
Br	Faeces	MS; ICP; HPLC	A method was developed to quantify metabolites of a Br-containing anti-tuberculosis drug in faeces by means of on-line ID, in combination with ESI-MS for their structural identification	53
Cd	Urine	MS; ICP; L	A novel application was reported for the determination of urinary proteins *via* a CdTe quantum dots label. The LOD for human albumin was 0.008 μg mL^{-1}	54
Cd	Human milk	AA; —; L	The geometric means of the concentration of Cd, Hg and Pb in breast milk from a sample of 100 Spanish women were 1.31 μg L^{-1}, 0.53 μg L^{-1} and 15.56 μg L^{-1}, respectively. Smoking and dietary habits were the main contributing factors	144
Ce	Human milk	MS; ICP; L	Ce concentrations were measured in human milk samples and paired serum samples from lactating women in Munich (Germany) and Madrid (Spain). No evidence of transfer from blood to milk was found	121
Cr	Saliva	AA; —; —; L	A retrospective study compared the levels of Cr and Ni in saliva from 28 subjects who had undergone fixed orthodontic therapy for 12–18 months with those observed in their same gender siblings selected as controls. A significant difference was observed for Ni levels, but not for Cr concentrations	98
Cr	Plasma, red blood cells, urine, hair	MS; ICP; L	The toxicokinetics of Cr in a case of accidental poisoning was followed by monitoring Cr concentrations in biological fluids, red blood cells and hair for 49 days. Evidence of *in vivo* Cr absorption into red blood cells and possibly other cells emerged	114
Cu	Kidney	MS; ICP; LA	The distribution of Cu, Pt and Zn in kidney from rats treated with cisplatin was determined as part of an investigation of Pt accumulation and renal damage	89
Cu	Pharmaceutical samples, serum	AA; —; —; L	An indirect method to determine adrenaline concentration in pharmaceutical and serum samples was reported, based on the reduction of Cu^{II} to Cu^{I} by adrenaline at pH 6.0, the subtraction of Cu^{I} from the solution by reaction with SCN^- to form CuSCN and the subsequent measurement of the remaining Cu^{II}. The LOD was 0.033 μg mL^{-1} and the RSD was 0.56%	116
Cu	Brain	AA; ETA; L	See Al, ref. 28	28
Cu	Tissue	MS; ICP; L	To assess the contribution of impaired Cu homeostasis to the oxidative stress in Alzheimer's disease (AD), post-mortem cortical tissue samples from AD cases and elderly controls were analysed for total Cu content, labile Cu concentration and capacity to stabilize Cu^{2+}	115

Table 1 (*Contd.*)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
Cu	Serum	MS; ICP; L	Based on a total of 2115 American, clinically healthy, children, mainly Caucasian, aged 0.5–18 years, reference ranges were proposed for serum Zn as 64–124 μg dL^{-1} and for serum Cu as 75–153 μg dL^{-1} (for children aged <10.3 years), 64–132 μg dL^{-1} (for those aged between 10.3 and 12.5 years) and 57–129 μg dL^{-1} (for children older than 12.5 years)	25
Fe	Mineral water	XRF; —; —	A clever sample pre-treatment, the precipitation of the stoichiometric K Li periodatoferrate complex, allowed to quantify trace amounts of Li, down to 1 μg, *via* the analytical determination of the more favourable element, Fe	72
Fe	Brain	AA; ETA; L	See Al, ref. 28	28
Gd	Urine, blood plasma	XRF; —; —	The determination of Gd was performed in urine and plasma samples from patients given Gd-based contrast agents prior to MRI and the results compared with those obtained by ICP-MS. LODs were 100 μg L^{-1} in urine and 80 μg L^{-1} in blood plasma, respectively	73
Gd	Blood, tissues	XRF; —; —	In ratmodels, Gd showed a rapid disappearance in blood, followed by a rapid and time-dependent accumulation in the liver. Bile was confirmed as the main elimination route for a Gd-based MRI contrast agent	93
Hg	Proteins	MS; ICP; LA	A novel approach, based on label-specific IDA, was applied to quantify ovalbumin labelled with ^{199}Hg enriched *p*-hydroxy-mercuribenzoic acid after PAGE. The LOD was 160 fmol (ovalbumin) and recovery was between 95% and 103%	79
Hg	Human milk	AA; —; L	See Cd, ref. 144	144
Hg	Blood	MS; ICP; GC AA; —; L	To determine the concentration of MeHg, blood samples (150 μL) were extracted with 6M HCl–NaCl, followed by derivatisation with $NaBPh_4$ and extraction into hexane, prior to analysis by GC-ICP-MS. The LOD was 86 ppt (as Hg). Total Hg was determined by AAS using the amalgamation technique	161
Hg	Urine	AA; CV; L	The results obtained, in mining areas in Zimbabwe, Indonesia and Tanzania, with portable mercury analysers, based on reduction with $SnCl_2$, were approximately 25% lower than those obtained on the same sample with laboratory equipment, using $NaBH_4$	119
Hg	CRMs	—; —; —	A review of the currently available environmental and biological CRMs for Hg speciation was presented	13
Hg	Brain	MS; ICP; L MS; ICP; HPLC	The mean concentrations of MeHg in brain from 24 polar bears were: 0.28 ± 0.07 mg kg^{-1} dw (frontal lobe), 0.23 ± 0.07 mg kg^{-1} dw (cerebellum) and 0.12 ± 0.03 mg kg^{-1} dw (brain stem)	162
Hg	Saliva	AFS; CV; —	A novel procedure, solidified floating organic drop microextraction, was applied for the pre-concentration of Hg from saliva samples. The DDC–Hg complex was extracted into 1-undecanol, which, after cooling in an ice bath, solidified in a microdrop. An enrichment factor of 182 was achieved from a 25 mL sample. The LOD was 2.5 ng L^{-1} and the RSD at 0.1 ng mL^{-1} was 4.1%	36
I	Single cell	MS; ICP; LA	LA-ICP-MS was applied to imaging of single cells and cell nuclei after iodination of fibroblast cells and thin tissue sections	90
I	Cow milk, human milk	MS; ICP; L	Over a period of 5 years, the content of I in cow (135) and human (65) milk samples in Thuringia (Germany), determined by ICP-MS after digestion with TMAH, remained stable	145
In	Urine	AA; ETA; L	After testing Amberlite IRC-50, Duolite GT-73 and Celite 545-AW, the pre-concentration of In from 100–200 mL urine samples was achieved by retention on 1.2 g of wet Chelex-100, followed by elution with 5.0 mL of 0.1 M HNO_3, with an LOD of 2.75 ng mL^{-1}	163
La	Serum	MS; ICP; L	A method was developed to measure serum La concentration in patients with chronic kidney disease administered with $La_2(CO_3)_3$. The LOQ was 0.1 μg L^{-1}	122
Li	Mineral water	XRF; —; —	See Fe, ref. 72	72

Table 1 (*Contd.*)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
Mg	Whole cells	XRF; —; —, AFM; —; —	A novel approach was reported, combining XRF microscopy and AFM, to obtain a concentration map for Mg in whole cells	95
Mn	Blood, plasma	MS; ICP; L	Modified skimmer cones were more successful than a collision cell to eliminate the FeH interference at mass 55 for the determination of Mn in blood and plasma samples, diluted with 0.005% Triton X-100, 0.2% propan-2-ol, 0.2% butan-1-ol and 1% HNO_3	48
Ni	Saliva	AA; —; —; L	See Cr, ref. 98	98
P	Liposomes	MS; ICP; CE	The simultaneous determination of P and Pt by means of CE-ICP-MS with Ar as the collision gas allowed to characterise a liposome-based formulation of oxaliplatin. The LOD was 29 ng mL^{-1} Pt and the RSD was 2.9%. A comparison was carried out with ICP-MS after microwave aided digestion	120
Pb	Blood	MS; ICP; L	An investigation of Pb isotopic ratios in environmental and blood samples allowed discriminating suspected sources of exposure in French children	164
Pb	Bone	XRF; —; —	An LOD of 43 ± 7 μg Pb g^{-1} was achieved for the *in vivo* determination of Pb in bone using a miniature X-ray tube with a silicon PiN diode detector	66
Pb	Roman medicines	XRF; —; —	Pb and Zn salts and other organic substances were identified in residues from medicine containers from Roman times analysed by GC-MS, XRF and Raman spectroscopy	165
Pb	Blood, hair, tissues	MS; ICP; L	The performance of a method for the simultaneous determination of both Pb concentration and isotope ratios (^{204}Pb : ^{206}Pb, ^{207}Pb : ^{206}Pb and ^{208}Pb : ^{206}Pb) in biological samples from exposed rats were reported. The concentration of Pb was calculated as the sum of all isotopes. The highest Pb concentration was in femur, followed by kidney, hair, liver and blood	166
Pb	Human milk	AA; —; L	See Cd, ref. 144	144
Pb	Bone	XRF; —; —, AA; ETA; L	The accumulation of Pb in bone was studied in an animal model (Wistar rats) exposed to Pb from birth	167
Pb	Bone	XRF; —; —; MS; ICP; L	XRF measurements of Pb performed by different laboratories on the same nine goat tibiae were compared with ICP-MS determinations	20
Pb	Blood, bone	XRF; —; —	Pb levels in blood and bone were found to be associated with several markers of cardiovascular disease, including tumour necrosis factor receptor-2, total cholesterol and HDL levels	168
Pb	Blood, plasma	MS; ICP; L	The kinetics of Pb in blood and plasma was studied in 5 cases of lead poisoning	169
Pb	Hair	MS; ICP; L	Three procedures for removing external Pb and Sr contamination from hair samples were compared. They were: centrifugation with diiodomethane; leaching with 2 M HNO_3 and washing with chloroform, MeOH and ultra pure water. Pb and Sr isotope ratios in scalp and facial hair were investigated in relation to geographical movements, in both archaeological remains and modern subjects	103
Pb	Teeth	MS; ICP; LA	The value of measurements of Pb in dentine was investigated by combining information of the spatial distribution of Pb with dental histology from *in utero* to several years after birth	117
Pd	Environmental and biological samples	MS; ICP; L	A micro-column packed with commercial thioureidopropyl functionalised silica gel was used for the pre-concentration of Pd and Pt from urine, serum and PM10 airborne particulate matter fraction samples, followed by microwave assisted elution with 0.5% thiourea. LODs of 0.2 ng L^{-1} and RSDs between 1.3% and 11.0% were achieved	40
Pt	Kidney	MS; ICP; LA	See Cu, ref. 89	89
Pt	Mononucleotides, dinucleotides, cellular DNA	MS; ICP; HPLC MS; ESI; —	*In vitro* studies of adducts of oxaliplatin with mono-nucleotides, di-nucleotides and cellular DNA were carried out using HPLC with both UV detection and coupled with SF-ICP-MS or ESI-MS. Pt was detected at concentrations as low as 0.14 ppb (0.22 Pt adduct per 10^6 nucleotides, based on a 10 μg DNA sample)	75 and 76

Table 1 (*Contd.*)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
Pt	Tissues, plasma	MS; ICP; L, AA; —; L	The levels of carboplatin–DNA adducts, measured in clinical samples removed 6 h after drug administration, ranged from 1.9 to 4.3 and 0.2 to 3.6 nmol Pt g^{-1} DNA for ovarian tumour biopsies and peripheral blood mononuclear cells, respectively. The reliability of the approach was validated on experimental animals	170
Pt	Liposomes	MS; ICP; CE	See P, ref. 120	120
Pt	Environmental and biological samples	MS; ICP; L	See Pd, ref. 40	40
Pt	Plasma, tissues	MS; ICP; L	The pharmacokinetics of a novel anticancer drug, dicycloplatin, was investigated in experimental animals	171
Rb	Urine	MS; ICP; L	In a study involving 240 women with incident invasive breast cancer before their treatments and 246 age-matched female controls, urinary levels of Rb were significantly and inversely associated with risk of breast cancer	123
S	Brain	XANES; —; —	2D-imaging of S species in tissue sections highlighted the presence of different (2−, 4+ and 6+) oxidation states	172
Sb	Plasma, tissues	MS; ICP; L MS; ICP; HPLC	The pharmacokinetics of meglumine antimoniate was investigated in monkeys. Sb levels were determined in timed collections of plasma as well as in tissues after sacrifice. The drug half-life was 35.8 days. Sb levels >1000 ng g^{-1} were found in thyroid, nails, liver, gall bladder and spleen	106
Sb	Hair, nails, teeth	—; —; —	A review of literature data confirmed the usefulness of hair Sb to monitor occupational exposure, but not as an index of health status. Few data were available for Sb concentrations in nails or teeth	105
Se	CRM (human plasma)	MS; ICP; LC MS; ICP; LA	The content of three selenoproteins (selenoprotein P, glutathione peroxidase 3 and selenoalbumin) was quantified using a combination of affinity LC-ICP-MS with on-line ID, LA-ICP-MS and MS/MS	23
Se	Nails	XRF; —; —	See As, ref. 71	71
Se	CRMs, serum	MS; ICP; HPLC	As a follow-up of a previously reported study for the quantification of SeMet by a primary method (species-specific ID-HPLC-ICP-MS), an investigation of the three main uncertainty sources was reported	19
Se	Liver, kidney	XRF; —; —	The distribution of Se in mouse liver and kidney was assessed by HR SR-XRF microscopy. A highly localized pool of Se at the basement membrane of kidneys was associated with glutathione peroxidase 3	94
Se	Proteins	MS; ICP; SEC	As part of investigations of a possible role of Se in the onset of cerebral vasospasm, metallomics techniques, including LC-MALDI-TOF/TOF and SEC-ICP-MS were applied to explore the proteome associated with the disease	51
Se	Urine	MS; ICP; LC	An investigation of the urinary excretion of selenite and selenate, enriched with ^{82}Se, given orally, highlighted differences in the metabolic pathways of these two Se species, with average excretions within 24 h of 33.7% selenate *vs.* 3.2% selenite	124
Se	Plasma	MS; ICP; HPLC	Heparin affinity chromatography used in combination with SEC allowed the retention of 90% of selenoprotein P from both and human plasma, but lacked specificity towards other human Se-containing proteins	173
Si	Ventricular whole blood	MS; ICP; L	The difference in Si concentration in whole blood from the left and right ventricles was reported as a marker of freshwater drowning. Si concentrations were determined by DRC-ICP-MS, after microwave assisted digestion with TMAH and H_2O_2	174
Sm	Mammary gland cells	TEM; —; —, SIMS; —; —	An investigation of the localization of Sm in mammary gland cells from lactating Wistar rats treated with Sm and controls indicated the preferential deposition of Sm in the epithelial cell lysosomes	97
Sr	Hair	MS; ICP; L	See Pb, ref. 103	103
Sr	Bone	XRF; —; —	Sr uptake in bones of an osteoporotic woman administered Sr citrate was monitored by means of XRF	67

Table 1 (*Contd.*)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
Ti	Serum	MS; ICP; L MS; ICP; LC	ID-double focussing-ICP-MS, with a medium resolution of 4000, was applied for the determination of the concentration of Ti in serum samples from 40 unexposed subjects (average concentration of 0.26 μg L^{-1}) and patients with Ti-based implants. The LOD was 0.05 μg L^{-1}. A study of the *in vivo* transport of Ti in serum by anion-exchange LC coupled on-line with double focussing-ICP-MS, using post-column ID for quantification, showed that 99.8% of the Ti present in serum was bound to transferrin	27
Ti	Blood	AA; ETA; L	The test samples were diluted 1+4 with 0.1% (m/v) Triton X-100. A chemical modifier, 200 μg NH_4NO_3–160 μg $Pd(NO_3)_2$, was used. An LOD of 0.2 μg L^{-1} was achieved. The working range spanned from 2 to 50 μg L^{-1} and the RSD was <12%	125
U	Tissues	TIMS; —; —	The concentrations of ^{234}U, ^{235}U, ^{236}U and ^{238}U and the isotopic ratios ^{234}U : ^{238}U, ^{235}U : ^{238}U and ^{236}U : ^{238}U were determined in 20 human tissue samples from a deceased subject, formerly occupationally exposed to U	56
U	Urine	MS; ICP; L	U levels in 24 h urine samples from volunteers of both genders, aged from 3 to 78 years, living in Southwest Nigeria, were determined. The median values for daily excreted U were 14.2 ng per day for adults and 45.1 ng per day for children, respectively, and were comparable to reference values for unexposed subjects in other countries	126
U	Hair	MS; ICP; L	The effect of external contamination was assessed by submitting hair samples from six adult volunteers to washing with water containing high levels of natural U. In the hair samples, cleaned according to widely used procedures before analysis, the U concentrations were about three orders of magnitude higher than in the original samples	127
Zn	Slug tissue	MS; ICP; LA	The distribution of Zn-containing proteins was mapped in whole tissue and in the proteins bands separated by one dimensional gel electrophoresis	77
Zn	Kidney	MS; ICP; LA	See Cu, ref. 89	89
Zn	Roman medicines	XRF; -; -	See Pb, ref. 165	165
Zn	Serum	MS; ICP; L	See Cu, ref. 25	25
Various (6)	Biological CRMs	XRF; —; —	The analytical capabilities of TXRF for the determination of low *z* elements (Ca, K, Mg, Na, P and S) in biological matrices were tested on CRMs after microwave assisted acid digestion. Additional preparation methods (direct analysis, microwave assisted acid digestion in micro-vessels, vapour-phase digestion on the TXRF carrier plates) were compared	34
Various	Biomedical samples	XRF; —; —	XRF-CT computed tomography was applied to the non-destructive imaging of the trace element distribution in biomedical samples, even of large size	175
Various (20)	Blood	MS; ICP; L	The expanded uncertainty of the results obtained by means of SF-ICP-MS ranged from 11% to 26%. LODs were between 0.0015 μg L^{-1} and 1.03 μg L^{-1}	18
Various (20)	Blood	MS; ICP; L	Concentrations of 20 elements were determined in blood samples from Italian adolescents, aged 13–15 years, by means of SF-ICP-MS	26
Various (4)	Blood	MS; ICP; L	Although largely recognised as a problem in the past, contamination of blood samples with Co, Cr, Mn and Ni from collecting devices was explored again	29
Various	Bone	XRF; —; —	Investigations of the elemental compositions of fossil bone and tooth specimens were performed with portable EDXRF spectrometers. To overcome the reduced accuracy of these instruments, statistical methods were applied, such as normalisation and mean centering of spectral data, before PCA	69

Table 1 (*Contd.*)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
Various (12)	Bone	XRF; —; —	The concentrations of Al, Br, Ca, Cl, Fe, K, Mg, Mn, Na, P, Sr and Zn were determined by EDXRF in bone samples from two burial sites from the 10th century AD. The results highlighted post-mortem environmental influences on the composition of bones as well as enhanced levels of Br and Sr accumulated during the past life	68
Various	Bone, cartilage	PIXE; —; —, PIGE; —; —	The distribution of trace and essential elements in human femoral head sections was investigated by PIGE (atomic number $z < 15$) or PIXE ($z > 15$) in relation to osteoarthritis	70
Various	Brain extracellular fluid, CRMs	MS; ICP; L	A system combining a small-bore PTFE sample loop, microdialysis sampling, on-line automatic in-loop SPE and ICP-MS was developed and its capabilities tested on CRMs and samples of brain extracellular fluid. LODs ranged from 0.003 to 0.5 μg L^{-1}	31
Various	Brain tissue	MS; ICP; LA	Human mesencephalon slices from a single subject, stored in formalin for more than 10 years, were analysed to provide information on elemental distribution	88
Various	Brain tissue	MS; ICP; L	To obtain maps of elemental distribution, small samples (from 0.014 to 0.338 mg) were obtained from selected brain areas by laser microdissection and digested in a closed vessel microwave oven prior to analysis	176
Various	Brain tissue	MS; ICP; LA	The technique capability to provide multielement information was exploited using specific data handling strategies and software	86 and 85
Various (8)	Brain tissue	MS; ICP; LA	The preparation of stable matrix-matched standards, based on ground rat tissue, spiked with the elements of interest and encapsulated in a tetraethyl orthosilicate sol–gel matrix was reported	87
Various (18)	Bronchoalveolar lavage fluid	PIXE; —; —	Out of 18 elements measured in bronchoalveolar lavage fluid samples from Holstein calves with mycoplasma bronchopneumonia ($n = 21$) and healthy controls ($n = 20$), the concentrations of Br, Ca, Fe, K, Mg, P and Zn were higher in diseased calves than in controls. The Cu : Zn ratio was proposed as a diagnostic aid	100
Various	CRM Bovine liver	MS; ICP; L	An improved sample introduction system, consisting of the combination of an inert loop injection unit with a high performance concentric nebuliser coupled with a temperature controllable cyclone chamber, allowed to introduce 20 μL samples in a carrier liquid flow of 10 μL min^{-1}, achieving the same sensitivity as conventional nebulisers	44
Various (6)	Gastric extracts	AE; ICP; ETV	ETV was applied to enhance the sensitivity of the determination of Ba, Co, Cu, Mn, Ni and Pb as part of an investigation of the bioavailability of these elements from airborne particulate matter. 700 mg synthetic gastric juice were added to four 12 mm diameter aliquots of each filter, corresponding to about 14.4 m^{-3} air. The sample was sonicated, then centrifuged. 40 μL of the exctract were placed in a graphite boat, dried in a laminar flow box using an infra-red lamp, then inserted in the graphite tube for analysis. LODs, determined on blank filters, ranged from 1.8 ng (Mn) to 12.2 ng (Cu) which corresponded to method LODs from 0.11 ng m^{-3} (Mn) to 0.75 ng m^{-3} (Cu). The RSD% varied from 1.9% (Cu) to 5.7% (Ni)	62
Various (5)	Hair	AA; F; L	The concentrations of Ca, Cu, Fe, Mg and Zn were determined in hair samples from 77 women aged 35.9 ± 9.7 years and compared with their daily intake of minerals	177
Various (17)	Single hair strands	MS; ICP; LA	Using a novel strategy, CRMs or in-house prepared matrix matched standards could be analysed under the same conditions as test samples, thus improving the quantification of As and 16 other elements and the detection of exposure time profiles. The LOD was 0.6 μg g^{-1} for As and ranged from 0.3 to 7.8 μg g^{-1} for the other elements	55

Table 1 (*Contd.*)

Element	Matrix	Technique; atomization; presentation	Sample treatment/comments	Ref.
Various (24)	Human follicular fluid	MS; ICP; L	After optimisation of analytical procedures for both Q- and SF-ICP-MS, 72 human follicular fluid samples were analysed	99
Various (4)	Human milk	AA; —; L	The concentrations of Cu, Mn, Se and Zn were measured in samples of human milk from Korean mothers of pre-term babies, collected over a period of 12 weeks post-partum. Both Se and Zn levels met the recommended daily requirements, whereas Cu intake from milk was lower and Mn intake higher	143
Various (5)	Muscle, bone	AE; ICP; L	The concentrations of Cu, Fe and Zn, measured in the muscle and bone tissues from the tail of an alligator (*Alligator mississippiensis*) were reported. Cd and Pb levels were below the LOD (0.5 μg g^{-1}) of the technique	155
Various	Nails	PIXE; —; —	3D elemental concentration maps of individual fingernails were obtained combining micro-PIXE and micro-RBS	96
Various	Pharmaceutical products	XRF; —; —, MS; ICP; L	TXRF was applied to the determination of metals, present as contaminants, in active pharmaceutical ingredients and intermediates. A comparison with ICP-MS was carried out for Cu and Pd determinations	74
Various	Proteins	MS; ICP; LA	A newly developed ablation cell for high spatial resolution analysis was tested on a protein sample after PAGE	84
Various (4)	Serum	MS; ICP; HPLC	The separation of Cu, Fe, Se and Zn species in 1 mL serum was achieved using monolithic anion exchange micro-columns and tandem HPLC-ICP-MS. The use of EDTA as anticoagulant was shown to influence the speciation of Fe and Zn	30
Various (64)	Serum	MS; ICP; L	Out of 64 elements measured in serum samples from patients with gouty arthritis ($n = 100$) and age-matched controls ($n = 40$), the concentrations of Al, Bi, Cu, Fe, Hg, Li, Se, Sr, Ta, Th, Ti and U were significantly altered in patients	102
Various (12)	Tissues, CRMs	XRF; —; —	Three sample preparation procedures were compared for the determination of As, Ca, Cr, Cu, Fe, K, Mn, Ni, P, Se, Sr and Zn by TXRF. Ultrasound-assisted extraction with a mixture of 10% v/v HNO_3–20–40% v/v HCl provided the best LODs	178
Various (5)	Tooth enamel, bone collagen	TIMS; —; — CFIRMS	Combined isotope measurement of C, N, O and S, by continuous flow isotope ratio-MS (CFIRMS), and of Sr, by means of TIMS, in human remains from a medieval Scottish village gave data from which information on their dietary habits and their capability to grow crops could be deduced	179
Various	Urine	MS; ICP; LA	The determination of several elements was achieved in a single droplet of urine, dried on supports such as Teflon sheets, Whatman 903 filter paper and glass slides, with LODs ranging from 0.003 to 0.58 μg g^{-1}	101
Various (5)	Urine	MS; ICP; L	The urinary levels of Be, Cd, Te and W were increased and that of Pb decreased in athletes *vs.* sedentary subjects	180
Various (5)	Urine RM	MS; ICP; L	An alternative sample introduction system, a dual drop-on-demand aerosol generator, and a calibration strategy based on the dosing frequency were applied to the determination of Cs, Li, Mo, Sb and Sr in urine in the concentration range of 8–122 μg L^{-1}	42

which led them to argue the appropriateness of blood Al determination as a marker for diagnosis of drowning.

It is pertinent to highlight concerns still raised over the *validity of published reference ranges for trace elements*. In response to concerns over the effect of low level Al exposure on childhood development, Zeager and colleagues[24] conducted a study to obtain information from clinical laboratories on reference ranges for Al in plasma, serum and urine. Significant variations were noted both in the ranges reported by the seven participating laboratories and in the ranges determined using different analytical techniques. For laboratories using AAS, the ranges varied from <5 μg L^{-1} to <20 μg L^{-1} for serum, <7 μg L^{-1} to 0–10 μg L^{-1} for plasma and 5–30 μg L^{-1} for urine, whilst, for laboratories using ICP-MS, values ranged from 0–6 μg L^{-1} to <42 μg L^{-1} for serum, 0–10 μg L^{-1} to 0–15 μg L^{-1} for plasma and 0–7 μg L^{-1} to 5–30 μg L^{-1} for urine. Perhaps more importantly, the authors noted that no ranges reported were known to be derived from studies of healthy infants and were developed from small-scale studies of either adult populations or sick children on parenteral therapy. The group concluded that further studies on Al concentrations in children were warranted in order to obtain data representative of a healthy infant population.

Erythropoietin (EPO) is used clinically to treat anaemia in chronic renal failure patients and pre-term infants.

Unfortunately, many *EPO formulations are contaminated with Al*. Viega *et al.*[104] coupled SEC with ETAAS to study the binding of Al to protein species in EPO formulations. With optimised conditions to separate EPO from serum albumin (also present as a major protein species), the authors quantitatively determined Al in 1 mL aliquots of the column eluate and established that Al was only associated with the fractions corresponding to the EPO peak. The researchers also examined the influence of temperature on Al binding to EPO and reported that the binding was three-fold higher at 37 °C than at 4 °C. In formulations containing 11 μg mL^{-1} EPO, approximately 50% of the Al was not ultrafilterable, from which they concluded that EPO was a very effective acceptor for Al.

5.4.2 Antimony. Filella *et al.*[105] presented a critical review of *the determination of Sb in hair, nails and teeth*. Their assessment focused on methodological approaches and the possibility of establishing reference ranges for Sb in these matrices. It was noted that the published data suffered from the lack of adequate CRMs to validate measurements and that many methods were insufficiently sensitive for quantitative determination of the element in these matrices. The researchers considered these limitations were responsible for the wide dispersion of published values and proposed a ceiling reference value of 0.1 μg g^{-1} for Sb in human hair. Despite these limitations and the well-recognised problem of external contamination of this sample type (see Section on Uranium), the authors concluded that the measurement of Sb in human hair was a useful method for monitoring occupational exposures to the element.

What is more certain is the *efficacy of Sb treatments for leishmaniasis*. A Brazilian group[106] examined the tissue deposition and elimination kinetics of Sb in monkeys infected with *Leishmania braziliensis* and administered low (5 mg Sb^V kg^{-1} body weight per day) and standard (20 mg Sb^V kg^{-1} body weight per day) doses of meglumine antimoniate. Levels of Sb in various tissues were determined using ICP-MS whilst IC coupled with ICP-MS was used to determine Sb speciation in plasma. Maximum plasma Sb concentrations were 27.4 ng g^{-1} and 95.7 ng g^{-1} for the low dose and standard dose groups respectively. Plasma Sb levels declined with a half-life of 35.8 days and the proportion of Sb as Sb^{III} rose from 5% to 50% during the first 9 days post-treatment. Tissue concentrations of Sb were highest in liver, thyroid, gall bladder and spleen. The authors considered that both the accumulation of Sb in these target organs and possible patho-physiological consequences of this accumulation were areas for further research.

5.4.3 Arsenic. Concerns over the high prevalence of chronic arsenicosis in regions of the Indian sub-continent do not appear to have abated if one considers the number of papers reporting on *human exposure to As* in these regions during this review period. The following papers suggest that the mitigation strategies put in place are not effective and that high exposures persist. Samal *et al.*[107] used FI-HG-AAS to determine As in groundwater and locally grown crops and vegetables from the Bengal delta region, whilst exposure to As was assessed by determining As in urine using the same analytical technique. The researchers measured exceptionally elevated concentrations in rice crops (194 μg kg^{-1} and 156 μg kg^{-1} in two different rice species) and estimated a daily As intake of 560 μg per day for adults and 393 μg per day^{-1} for children, which was supported by the levels of As determined in urine samples (154–276 μg L^{-1}). The authors concluded that more action was needed to be taken to control contamination of the local food supply and thus protect the population who are consuming these foods. Gardner *et al.*[108] reported the findings of a longitudinal study of As exposure in mother–child pairs from rural Bangladesh. The mothers were monitored in early gestation and subsequently with their children through to five years post-partum. Urine As concentrations were quantitatively determined using HPLC coupled on-line with HG-ICP-MS. Children at five years had elevated levels of As (16–355 μg L^{-1}) and these showed a significant positive correlation with levels at 1.5 years and to maternal concentrations in early gestation. The results led the researchers to conclude that exposure to As remained high despite the mitigation strategies that had been introduced to date. The group proposed that further strategies need to be adopted and rigorously monitored and evaluated. The Indian sub-continent is not the only region that suffers from high environmental As levels. Cubadda *et al.*[109] investigated urinary As excretion in an adult population living in Latium, Central Italy, a region which also has elevated levels of As in groundwater and locally grown produce. The researchers rightly re-emphasised the fact that total urine As is not suitable for biological monitoring of iAs exposure. Five As species were quantitatively determined in urine using gradient elution anion exchange HPLC-ICP-MS. Relative proportions of the major species were iAs 14%, MMA 13% and DMA 72%. Total As levels ranged between 2 and 72 μg L^{-1}. The dimethylthioarsinic acid species was also detected in 33% of the samples analysed at concentrations ranging from trace levels to 6 μg L^{-1}.

One of the more important papers on As speciation presented over this review period was that of Alava *et al.*[110] The group were interested in how the gut microflora influence *As metabolism in humans* and, to investigate this, they developed a simulated human intestinal microbial environment. A combination of anion exchange HPLC with ICP-MS was developed to separate and quantitatively determine As^{III}, As^V, DMA^V, MMA^V and monomethylmonothioarsenate, whilst a C_{18} column was used to separate MMA^{III} and DMA^{III} species. The methods were used to determine As species in suspensions sampled from the *in vitro* simulator and also *in vivo* from faeces and samples taken from the human colon. A second group[58] undertook a series of *in vitro* experiments to study the synthesis of possible intermediates of As metabolism. In particular, the researchers investigated the reaction of methylated As species with biomolecules such as glutathione and *S*-adenosylmethionine through protein thiol–As bonds. The As species generated by the *in vitro* reactions were identified using ESI-MS and HR-MS and from the results obtained they hypothesised a number of non-enzymatic chemical reactions that may play a role in intracellular As metabolism. One might question whether these reactions monitored *in vitro* truly reflect *in vivo* metabolic reactions or are simply artefactual consequences of the particular conditions employed in the experiments.

5.4.4 Beryllium. The quantitative determination of *trace concentrations of Be in biological matrices* using ICP-MS often

involves some form of sample treatment to pre-concentrate Be from the sample matrix prior to measurement of the element. In an effort to avoid the need for element pre-concentration, Lariviere *et al.*[43] combined a high matrix interface configuration with internal standardisation to quantitatively determine Be in diluted samples of human autopsy tissue digests. Optimisation of the interface configuration enabled the system to deal with the high salt and dissolved solids within the digested samples and gave a reported 2.7-fold improvement in LOD (0.6 μg L^{-1}). The method was validated by determining Be concentrations in hair and blood CRMs. The authors used the method to determine Be levels in autopsy samples from the US *trans*-uranium and uranium register. Beryllium concentrations between 0.015 and 255 μg kg^{-1} were reported for the autopsy samples analysed.

5.4.5 Bismuth. Recent ASU reviews have reported on *trace element pre-concentration procedures based on liquid–liquid microextraction* methods. Two research groups reported such methods for the pre-concentration and quantitative determination of Bi in biological matrices. Fayazi *et al.*[111] used 2-(5-bromo-2-pyridylazo)-5-(diethyl amino)phenol as the complexing agent with acetone and dichlorobenzene as the dispersing and extracting solvents respectively for the extraction of Bi^{3+} followed by determination using FAAS. Using optimised concentrations of complexing agent and extraction solvent, the researchers reported an enrichment factor of 28.6 giving an LOD of 3 ng mL^{-1} with RSD of 1.5% at 0.4 μg mL^{-1}. The authors used the method to determine Bi in a range of natural and spiked biological materials. For the cloud-point extraction of Bi from human serum, Sun and Wu[112] used 8-hydroxyquinoline as the complexing agent and Triton X-114 as the ionic surfactant. The authors optimised extraction conditions to achieve an 81-fold enrichment factor from an initial 25 mL sample volume. This does, however, seem to be a rather excessive blood sample volume to be taken from human subjects. The concentration of Bi^{3+} in extracts was determined using ICP-AES. An LOD of 0.12 μg L^{-1} was reported.

5.4.6 Boron. The WHO guideline value for *B in drinking water* (0.5 mg L^{-1}) is designated as provisional because of the difficulty in achieving it in areas of high natural B levels. The pertinence of this statement is exemplified in the work undertaken by Cortes *et al.*[113] The researchers determined levels of B in tap and bottled water from a region of Northern Chile and corresponding levels of B in urine from a volunteer population drinking this water. Urine and water concentrations of B were determined using ICP-AES. Levels of B in tap water ranged from 0.22 mg L^{-1} to 11.3 mg L^{-1} and in bottled water from 0.01 mg L^{-1} to 12.2 mg L^{-1}. Urine B concentrations ranged from 0.45 mg L^{-1} to 17.4 mg L^{-1} with a median value of 4.28 mg L^{-1}. A positive correlation was observed between urine B and tap water B levels in the houses of the volunteers. The group strongly recommended that water B levels be monitored in Northern Chile and that regulatory standards be introduced to limit exposure and protect public health.

5.4.7 Bromine. Human studies of drug metabolism and elimination often necessitate the use of a ^{14}C radiolabelled analogue of the drug for *quantitative determination of drug metabolites*. To avoid this exposure risk, Meerman and colleagues[53] investigated the application of HPLC coupled with both ICP-MS and ESI-MS to monitor the elimination of Br species in faecal samples from subjects administered a bromine-containing anti-tuberculosis drug (TMC207). Quantitative determination of Br species was performed using on-line ID-ICP-MS, whilst structural information on the Br species was obtained using ESI-MS. The reported LOD for the drug was 1.5 mg L^{-1} which was the same order of magnitude as that for radio-detection methods. The authors concluded that the analytical figures of merit supported the application of this approach rather than one using a radioisotope.

5.4.8 Cadmium. Whereas past ASU clinical reviews have always tended to focus on the toxicity of Cd to biological systems, this review sees a completely different aspect of Cd determination being reported where Cd was used as an elemental tag to quantitatively determine very low levels of total protein in human urine.[54] Determination of urinary proteins has conventionally been performed using colorimetric assays. In this novel approach, the researchers used CdTe quantum dot nanoparticles to label urinary proteins for indirect quantitative determination using ICP-MS. The workers considered CdTe nanoparticles to have outstanding properties for such measurements, having high sensitivity afforded by the large number of detectable atoms within each nanoparticle tag. Urine proteins were directly conjugated with the nanoparticles by incubation in wells of micro-titer plates. After washing, the protein–nanoparticle conjugate was dissolved in 5% HNO_3 and diluted 15-fold in 1% HNO_3 for quantitative determination of Cd. An LOD of 0.008 μg mL^{-1} for human serum albumin was reported and a wide linear range extending to four orders of magnitude. The method was assessed by comparing results obtained for 50 urine samples using the tagging method with those using a hospital reference method based on colorimetric assay. Good agreement ($r = 0.988$) was reported between the two methods.

5.4.9 Chromium. It is not often that this review covers incidents of *acute metal poisoning*. However, the case reported by Goulle *et al.*[114] merits comment because of its positive outcome. Following accidental ingestion of a 30 g L^{-1} $K_2Cr_2O_7$ solution (estimated 3 g Cr ingested), the patient was admitted into hospital intensive care where whole blood, plasma, urine and hair Cr levels were monitored using ICP-MS. The patient was monitored for 7 days after which he was discharged from intensive care with no evidence of renal or liver failure. Levels of Cr in body fluids and hair were monitored for a further 42 days. Over this period, plasma Cr declined from a peak of 2088 μg L^{-1} to 5 μg L^{-1}, blood Cr from 631 μg L^{-1} to 129 μg L^{-1} and hair Cr from 3512 μg g^{-1} to 10 μg g^{-1}. This individual clearly had very effective metabolic processes for dealing with biologically active Cr^{VI} and reactive oxygen species and the biotransformation of Cr^{VI} to Cr^{III}, which would have been worth investigating further.

5.4.10 Copper and zinc. With continuing developments in analytical techniques and changes in environmental exposures and dietary habits, it is pertinent to continue to review *reference intervals for essential trace elements in 'vulnerable' populations*. Lin *et al.*[25] reported reference intervals for Cu and Zn in serum from a healthy American paediatric population. Serum Cu and Zn were determined using ICP-MS and statistical analyses performed using STATA software. The researchers reported a significant

difference in Cu reference levels in different age groups but this relationship was not observed with Zn. Age-dependent reference intervals for Cu were 75–153 μg dL^{-1} for ages <10 years, 64–132 μg dL^{-1} for ages 10 to 12.5 years and 57–129 μg dL^{-1} for ages >12.5 years. The reference interval for Zn was 64–124 μg dL^{-1}.

An Australian research team[115] presented work that implied *a role for labile Cu in the pathogenesis of Alzheimer's disease*. The researchers used ICP-MS to determine total concentrations of Cu in post mortem cortical tissue from Alzheimer's disease patients and non-dementia control subjects. The group also determined the proportion of labile Cu using a Cu–phenanthroline assay and the level of oxidative tissue damage by measuring the presence of thiobarbituric acid-reactive compounds. It was observed that both total Cu and labile Cu were elevated in the Alzheimer's disease group and also noted that cortical tissue from this group had a greater capacity to bind Cu^{2+}. The hypothesis was presented that the observed changes reflected a breakdown of Cu homeostasis in Alzheimer's disease.

Becker *et al.*[77] conducted a metallomic study of *intracellular Zn distribution and Zn-protein binding* in slugs, which are commonly used as a monitoring organism for environmental contamination. Intracellular localisation of Zn was determined using LA-ICP-MS. Protein binding of Zn was also determined using LA-ICP-MS following one dimensional separation of proteins by PAGE. The researchers observed that Zn was detected in three prominent bands at 75, 100 and 150 kDa. Efforts were made to identify the proteins using MALDI-TOF-MS analysis of tryptic digests but no matches with previously characterised mollusc proteins were made.

A number of papers in this review period describe spectrometric methods *to determine trace elements used as probes to indirectly determine other biomolecules* (see also Section on Cd). In the method described by Zheng *et al.*,[116] the measurement of Cu^{II} using AAS was used to indirectly determine concentrations of adrenaline in serum samples and pharmaceutical preparations. The method relied on the reduction of Cu^{II} to Cu^{I} by adrenaline in the presence of SCN^- and the formation of a CuSCN emulsion. Measurement of the residual Cu^{II} was used to calculate the concentration of adrenaline in the sample. The authors reported that the method could quantitatively determine adrenaline concentrations between 0.08 and 6 μg mL^{-1}. It is open to question whether the specificity and sensitivity of these indirect methods matches those of methods developed to directly measure the biomolecule of interest.

5.4.11 Gold. Although *gold-based drugs have been used therapeutically for more than 40 years* in the treatment of rheumatoid arthritis, little is still known about its mode of action. Albert and colleagues[52] described the development of methods coupling LC with ESI-MS and ICP-MS to characterise and quantitatively determine Au species generated by reaction between the drug Auranofin and glutathione or human serum albumin. It was observed that Auranofin undergoes ligand exchange and the triethylphosphine-gold species covalently binds to both biomolecules and proposed this as a potential reaction pathway for the drug.

5.4.12 Iodine. Over the 25 years that the ASU review series has been published, the advancements in instrumentation have led to opportunities to develop methodologies to determine *elemental concentrations and distributions at the cellular and intracellular level* rather than the macroscopic organ and tissue level. This is exemplified in the paper by Giesen and colleagues[90] who developed a method to determine I in fibroblast cells and thin tissue sections using LA-ICP-MS. It was observed that, following incubation of cells and tissue sections in an I solution for 60 s, I was preferentially located in cell nuclei. Spatial resolution was reported to be sufficient to detect small cell nuclei in liver biopsy tissue sections. The group also investigated the use of I as an internal standard to correct for tissue inhomogeneity in the simultaneous determination of two breast tumour markers (Her2 and CK7).

A comprehensive review of recent literature on *methods to determine I in environmental, biological and clinical matrices* was undertaken by Moreda-Pineiro and colleagues.[15] The review covered different sample pre-treatment methods to extract total I as well as specific I species. It examined the most commonly used techniques for the determination of total I and the coupling of chromatographic and electrophoretic methods to spectrophotometric instrumentation for I speciation.

5.4.13 Lead. Each review period always sees a significant number of papers reporting *the determination of Pb in bone using XRF*. Yet, in contrast with the enormous amount of effort expended in developing interlaboratory comparison and proficiency testing schemes to improve the measurement of Pb in blood, this review reports on the first publication of work to compare the performance of different laboratory systems undertaking *in vivo* bone Pb measurements using XRF. Bellis *et al.*[20] circulated samples of 9 goat tibiae to 15 laboratories performing bone Pb measurements with XRF instruments and who had agreed to participate in the exercise. The bone samples had mean Pb concentrations ranging between 1.8 μg g^{-1} and 35.8 μg g^{-1} Pb dw, as determined by a reference method using ICP-MS. The intercomparison exercise revealed that 8 of the laboratories showed no analytical bias for any of the samples whilst the remaining 7 laboratories reported biases for between one and six of the nine samples distributed. To investigate the performance of a novel miniature XRF system for determining Pb in bone, Fleming and colleagues[66] constructed sets of bone phantoms from plaster of Paris doped with varying concentrations of Pb. Both round and square cross-sectional surfaces were prepared and, to simulate the *in vivo* scenario of overlying soft tissue, the team placed thin resin films between the phantom and the XRF instrument. The reported LOD for a circular cross-sectional phantom with a resin layer of 2.7 mm was 43 ± 7 μg g^{-1}.

Work is continuously being undertaken to identify *valid biomarkers of early Pb exposure* as alternatives to blood Pb determination. Shepherd *et al.*[117] used the high spatial resolution capability of modern LA-ICP-MS instrumentation to examine the concentration of Pb in circumpulpal dentine of deciduous teeth in order to investigate the exposure of infants to this toxic element. By combining the Pb measurements with histological data and a true time line of dentine growth, the authors argued that meaningful exposure histories could be obtained from a single ablation transect on longitudinal

sections of individual teeth, each Pb measurement representing a time span of 42 days. They correctly highlighted the dangers of translating these measurements into blood Pb estimations without a reliable history of the tooth sample, and were undertaking further work to validate the method as a blood Pb biomarker.

5.4.14 Magnesium. Following the rapid advances in metallomics, researchers are continuing to look at combinations of sensitive techniques to elucidate *intracellular spatial distribution of trace elements*. Lagomarsino *et al.*[95] combined the use of two nanoprobe methods to investigate intracellular concentrations of Mg. The concentration distribution of Mg was derived by normalising the spatial distribution determined using XRF microscopy to the cellular thickness determined using atomic force microscopy. The authors argued that the marked differences between elemental distribution and the normalised concentration maps indicated that the normalisation procedure was essential to obtain reliable information regarding the functional role of elements in whole cells.

5.4.15 Manganese. Many recently published methods for the determination of trace elements in biological matrices using ICP-MS have relied on *collision cell technology to eliminate interferences from polyatomic species*. However this technology may not be effective for every element of interest. Richardson *et al.*[48] examined the use of collision cell technology to overcome interferences from FeH on the quantitative determination of Mn in plasma and whole blood. It was established that the interference from FeH on ^{55}Mn was not eliminated by this approach. However, the interference was successfully overcome by modifying the geometry of the skimmer cones of the ICP-mass spectrometer. With this modified geometry, Mn was quantitatively determined in blood and plasma samples following dilution of the samples with 0.005% Triton X-100, 0.2% propan-2-ol, 0.2% butan-1-ol and 1% HNO_3 and addition of Ga as an internal standard.

5.4.16 Mercury. Kutscher *et al.*[79] used *p*-hydroxy-mercuribenzoic acid to label ovalbumin for *indirect quantitative determination through the measurement of Hg using LA-ID-ICP-MS*. The protein was labelled with ^{199}Hg-enriched *p*HMB and subjected to PAGE for ablation analysis of the protein bands. No loss of Hg label was noted during any of the sample preparation steps. The researchers compared the data obtained using ID with an external calibration method based on the derivatised protein and considered the ID method to be more precise and sensitive, with a reported LOD of 160 fmol protein. It was also regarded that the ID method was more reliable where complex protein separation protocols were used.

Guzman-Mar *et al.*[118] described a novel method for Hg speciation analysis based on multi-isocratic elution chromatography coupled with CV-AFS. A multi-syringe configuration was used to separate iHg, MeHg and EtHg using a RP C_{18} column and two phase chromatographic elution with 0.005% mercaptoethanol in 240 mM CH_3COONH_4–C_2H_3N (99 : 1 v/v) followed by 0.005% mercaptoethanol in 240 mM CH_3COONH_4–C_2H_3N (90 : 10 v/v). Eluted Hg species were oxidised by UV irradiation and Hg released by reaction with $SnCl_2$ for determination using AFS. The reported LODs were 0.03 μg L^{-1}, 0.11 μg L^{-1} and 0.09 μg L^{-1} for MeHg, iHg and EtHg, respectively. The method was validated by analysing DORM-2 CRM. A very novel sample preparation method was described by Yuan *et al.*[36] for the quantitative determination of Hg in human saliva by AFS. Mercury was complexed with DDC and extracted into fine droplets of 1-undecanol. The extract was then chilled on ice to solidify the droplet into a single ball floating on top of the solution. The ball was transferred to the CV-AF spectrometer for determination of Hg. Concerns over the merits of salivary measurements for monitoring exposures to toxic elements have been previously highlighted and the applicability of this method for clinical monitoring is questionable given the size of the saliva sample required (25 mL !).

Monitoring occupational exposure to Hg is still extremely important in areas where it is used in small scale gold mining and extraction industries. Interest has previously been shown on the development of portable analysers for field measurements of Hg in environmental and biological matrices. Baeuml *et al.*[119] investigated the use of two portable Hg analysers for monitoring Hg in urine of subjects living in mining regions of Zimbabwe, Tanzania and Indonesia. Urine samples collected from volunteers were firstly analysed at the sampling site using two different CV-AAS systems and then in a controlled laboratory environment using a conventional bench top Hg analyser. The researchers recorded that values determined by the portable systems were on average some 25% lower than those determined by the stationary system, which may have been due in part to the use of different reducing agents ($SnCl_2$ for the portable system and $NaBH_4$ for the laboratory system). Even so they argued that the mobile system has a useful role in screening populations where environmental exposure to Hg is an issue. It would appear that further work needs to be done on developing methods for portable instruments that give consistent results with laboratory-based systems.

5.4.17 Platinum. *The focus for Pt continues to lie with its use in anti-cancer treatment* and the monitoring of drug administration, intracellular distribution and elimination. Nguyen *et al.*[120] used CE-DRC-ICP-MS to separate and quantitatively determine free oxaliplatin from liposome-entrapped drug in a novel drug formulation. Interferences in the determination of Pt were suppressed by using Ar as the collision cell gas. An LOD of 29 ng mL^{-1} was reported. The authors compared the results for free and encapsulated Pt determined using this method with those for total Pt following microwave digestion of the drug formulation and found good agreement. They considered the CE-ICP-MS method to be valuable for the *in vitro* characterisation and quality assurance of liposome-based metallodrugs.

The *Pt-based chemotherapeutic drugs exert their cytotoxic action through formation of DNA adducts* and work continues to be undertaken on the identification and quantitative determination of these adducts in tumour cells and tissues. A research group from Loughborough University reported two studies on the determination of Pt–DNA adducts and subcellular localisation of Pt in human cancer cells. In the first,[76] the group described a method for the sensitive determination of Pt–DNA adducts in human carcinoma cell models using SF-ICP-MS. Cells were incubated with either oxaliplatin or cisplatin,

harvested and then either the DNA extracted or the cells fractionated into four sub-cellular compartments. Samples were digested for quantitative determination of Pt. Subcellular distribution of Pt for cisplatin treated cells was 70% in cytosol, 17% in the membrane fraction, 9% in the nuclear fraction and 4% in the cytoskeleton fraction. In the second,[75] the researchers coupled HPLC with ESI-MS and SF-ICP-MS to study the *in vitro* formation of Pt–DNA adducts following reaction of oxaliplatin with mononucleotides, di-nucleotides and cellular DNA. With optimised chromatographic conditions, five Pt adducts were formed in the reaction of oxaliplatin with mononucleotides and three adducts in the reaction with di-nucleotides. The method was also used to quantitatively determine oxaliplatin intra-strand DNA adducts in human colorectal cancer cells. With a reported LOD of 0.14 ppb Pt, the authors considered the method suitably sensitive for assessment of adduct formation in patients undergoing oxaliplatin chemotherapy. Unfortunately, a serious side-effect of Pt-based drugs is their nephrotoxicity. For this reason, Moreno-Gordaliza and colleagues[89] studied the cellular deposition of Pt in kidney tissues of rats administered pharmacological doses of cisplatin. Platinum was quantitatively determined in 3 μm sagittal sections of kidney using LA-ICP-MS and was found to accumulate in the cortex and cortico-medullary region. The researchers also noted that Pt accumulation was dramatically reduced when cilastatin was co-administered with cisplatin, which they considered reflected its nephroprotective effect. The high analytical sensitivity (LOD = 50 fg) and excellent spatial resolution led them to conclude that the method was very well suited for investigation of metal interactions at the intracellular level.

5.4.18 Rare earth elements. Although papers on the determination of REEs regularly appear in this ASU Review series, over the past 20 years there has never been a paper specifically describing *the determination of Sm in clinical or biological matrices* until now. Concerns over the increasing use of REEs in medical and industrial applications led Ahlem *et al.*[97] to investigate the intracellular localisation of Sm in mammary tissue of lactating Wistar rats following administration of the element. The group used TEM and SIMS to reveal the presence of Sm-rich deposits in the lysosomes of epithelial cells from the mammary glands. No Sm-rich deposits were observed in the untreated control group. It was concluded that lysosomes were the sites of intracellular accumulation of foreign elements, including the REEs and hypothesised that the Sm deposits were composed of insoluble phosphates.

It was similar concerns over *the exposure to the general population to Ce* from the growing industrial use of Ce and use of CeO_2 nanoparticles as a diesel fuel additive that led Michalke and colleagues[121] to investigate whether there was an increased risk of nutritional exposure for breast-fed babies due to transfer of Ce from maternal blood into breast milk. The group developed a method for the quantitative determination of Ce in serum and breast milk using ICP-MS. Breast milk samples from subjects in Munich and Madrid had similar median Ce concentrations of 13 ng L^{-1}, whereas serum Ce concentrations were higher in the Madrid study group (21.6–70.3 ng L^{-1}) compared with the Munich group (<10 ng L^{-1}). The researchers observed no enrichment of Ce in milk from maternal blood and concluded, therefore, that there was no increased exposure risk for breast-fed babies.

The increasing *use of Gd-based MRI contrast agents in medical diagnoses* has encouraged the development of simple and rapid methods to determine Gd in blood and urine samples to monitor the Gd dose administered and the kinetics of elimination in patients undergoing MRI. Telgmann *et al.*[73] investigated TXRF as an alternative to more conventional ICP-MS for the quantitative determination of Gd in human body fluids. The method was evaluated by comparison with measurements made using ICP-MS. Limits of detection of 100 μg L^{-1} and 80 μg L^{-1} were reported for urine and plasma respectively and the author considered the method to be an attractive alternative to ICP-MS for clinical laboratories undertaking Gd measurements in biological matrices. A second group from the University of Trieste[93] also described the use of SR-XRF at both the macro and microscopic level to determine the hepato-biliary deposition of a Gd-based MRI agent in *ex vivo* model systems.

Handley and colleagues[122] considered many published methods for *the determination of La in biological samples* to be unsuitable for routine use due to complicated and aggressive sample pre-treatments. For this reason they developed a simple method for the determination of La in serum using ICP-MS. The method was used to measure serum La concentrations in patients administered $La_2(CO_3)_3$ as a phosphate binder for stage V chronic renal disease. The reported LOQ was 0.1 μg L^{-1} and in all samples analysed from subjects not receiving $La_2(CO_3)_3$, the concentration of La was below the LOQ. Even in subjects receiving doses of 500–1500 mg per day only 12 samples out of 20 had quantifiable concentrations of La. The results indicate that there is no accumulation of La in patients administered the agent but does suggest that some form of sample treatment is required to improve analytical sensitivity for the analysis of this element in biological matrices.

5.4.19 Rubidium. Since the publication in 1984 of research suggesting *Rb has anti-cancer activity* through the raising of intracellular pH, there has been little further work to substantiate or refute the hypothesis. However, some interest appears to have been reignited with the work described by Su *et al.*[123] The group investigated the relationship between urinary Rb concentrations and incidence of breast cancer. Urine samples were collected from 240 women with invasive breast cancer and 246 age-matched controls. Urine Rb was quantitatively determined using ICP-MS. The creatinine-corrected median, 25th and 95th percentile values were 2253, 16 068 and 3110.5 μg g^{-1} creatinine for the cancer group compared with 2921.9, 2367.9 and 4142 μg g^{-1} creatinine in the control group. After adjusting for confounding risk factors the authors hypothesised that urinary Rb was significantly and inversely associated with breast cancer risk and considered determination of urine Rb as a potential biomarker for breast cancer risk. It will be interesting to see if this recent publication stimulates further work to establish any anti-cancer role for Rb in humans.

5.4.20 Selenium. The enormity of the challenge in trying to interpret the biological significance of the multitude of selenium species so far identified in different biological matrices

was brought home by the report of Preud'homme *et al.*[50] who presented a comprehensive cartography of Se metabolites synthesised during the enrichment of yeast with Se^{IV}. They reported the detection of 49 compounds using on-line SEC with both ICP-MS and ESI-MS. Ballihaut and colleagues[23] presented an important systematic study to establish quantitative values for the major selenoproteins, selenoprotein P, glutathione peroxidase 3 and selenoalbumin in NIST SRM 1950 Metabolites in Human Plasma. The researchers used a combination of on-line ID affinity chromatography-ICP-MS, LA-ICP-MS and tandem MS to identify and quantify the three Se containing species and reported values of 50.2 ± 4.3 ng g^{-1}, 23.6 ± 1.3 ng g^{-1} and 28.2 ± 2.6 ng g^{-1} as Se for selenoprotein P, glutathione peroxidase 3 and selenoalbumin respectively. A study by Gammelgaard *et al.*[124] also indicated that Se metabolism in humans is a complex process. The group used LC-ICP-MS to investigate the urinary excretion of Se species following sequential oral administration of ^{82}Se labelled selenate and selenite to seven healthy volunteers. The volunteers were given a solution of selenate containing 74.3 μg ^{82}Se and urine samples collected over the next 24 h. The same procedure was followed, after a four week gap, with administration of a solution of selenite containing 74.4 μg ^{82}Se. The authors reported that the mean total urinary excretion of Se after selenate administration was 33.7% compared with only 3.2% following selenite administration. The researchers also noted that, in six of the volunteers, the majority of the Se excreted following selenate administration was unchanged, whilst in one volunteer some 20% had been converted to selenosugar. It may be concluded that selenate and selenite are metabolised by different pathways.

Malinouski *et al.*[94] used XRF to map *the cellular distribution of Se* in mouse liver and kidney. They observed that Se was uniformly distributed in liver tissue whereas in kidney there were both areas of uniform Se distribution but also localised areas of high Se concentration. The main areas of localised high Se were the proximal tubules. By studying the Se distribution in mouse strains deficient in either selenoprotein P or glutathione peroxidase, they established that the proximal tubule localised Se was associated with glutathione peroxidase.

5.4.21 Thallium. Thallium is used in various specialised industries including optics and electronics, but has gained particular historical notoriety through some high profile deliberate poisonings. Because of its industrial and nefarious uses, methods have continuously been developed *to determine concentrations of Ti in biological matrices* in order to monitor occupational exposure or assess accidental or deliberate intoxication. Solovyev and colleagues[125] described a method for the direct determination of Ti in whole blood using ETAAS with high frequency modulation polarisation Zeeman background correction. Sample preparation was a simple five-fold dilution with 0.1% Triton X-100. Matrix interferences were overcome by using a rhodium treated L'vov platform and an NH_4NO_3–$Pd(NO)_3$ chemical modifier. The method was assessed by analysing a human plasma SRM and spiked blood samples, and an LOD of 0.2 μg L^{-1} was reported.

5.4.22 Titanium. The continuing expression of concerns over increasing serum concentrations of metal degradation products from titanium based orthopaedic implants led the research group of Sanz-Medel at Oviedo University[27] to develop a sampling strategy and analytical method for the quantitative determination of total Ti in human serum using ID-ICP-MS in order to establish the basal level of Ti in populations with and without orthopaedic implants. By minimising sample handling and pre-treatment, an LOD of 0.05 μg L^{-1} was achieved, which permitted the researchers to establish a mean Ti concentration of 0.26 μg L^{-1} in a control population ($n = 40$). The authors compared this background level with those found in groups of patients with different Ti implants. Coupling anion-exchange LC with double-focussing ICP-MS also enabled the group to establish that 99% of serum Ti was bound to serum transferrin.

5.4.23 Uranium. Nigeria is a principal area for mining of U. Hollriegl *et al.*,[126] therefore, considered it important to establish *a baseline value for urine U* in non-exposed Nigerian populations in order to better assess cases of environmental exposure from mining activity. They determined U in 24 h urine samples collected from adult and child volunteers in a low environmental U region of SW Nigeria. Urine U was determined using ICP-MS and corrected for creatinine concentration. The median and range determined in adults were 33.4 ng g^{-1} and 2.52–252.7 ng g^{-1}, respectively. The median value was higher in children under 15 years (76 ng g^{-1}). These values were consistent with those determined for non-exposed populations in other countries and the authors, therefore, considered them to be appropriate as baseline values for the Nigerian population.

The work of Muikku and Heikkinen[127] re-emphasised the importance of using *the correct biological matrix for monitoring human exposure to toxic elements.* The researchers investigated the perennial debate of distinguishing external contamination from internal element incorporation in human scalp hair by examining the exogenous binding of U to hair from uranium-rich household water. After incubating hair samples in the uranium-rich water, the samples were washed using two commonly used washing procedures and residual U determined using ICP-MS. The authors noted that, even after washing with well established procedures, hair U concentrations were still three orders of magnitude above the levels determined before incubation with uranium-rich water. As has been stressed in this review before, they concluded that great care needs to be taken when using hair as a biomarker of the internal dose of exposure.

6 Applications: drugs and pharmaceuticals, traditional medicines and supplements

A comparison of TXRF with other techniques for the measurement of residual metals in active pharmaceutical ingredients, by Antosz *et al.*[74] was discussed in Section 4.5.2. While this application may develop in importance in the future, for the moment other techniques are more usually employed to analyse *therapeutic agents*. Concentrations of adrenaline in pharmaceuticals and also in serum samples were determined using AAS by Zheng *et al.*[116] This was achieved by exploiting the reaction between a known amount of Cu^{2+} and adrenaline in the presence of SCN^-. Reduction of the copper to Cu^+ occurs with

formation of CuSCN as a white emulsion which is then removed. Measurement of the residual Cu^{2+} provided an indirect determination of the concentration of the adrenaline. Delivery of drugs to the site where they exert their effective action, without causing side effects, is the ideal therapeutic treatment. However, this is not easily achieved. One approach that has attracted a lot of interest, particularly for anti-cancer drugs, is to encapsulate the agent within phospholipid particles known as liposomes. A liposomal-oxaliplatin formulation was investigated by Nguyen *et al.*[120] to assess how much free oxaliplatin remained in prepared material. Capillary electrophoresis coupled to ICP-MS was used to separate the free drug from that within the liposomes and for the simultaneous measurement of P and Pt. Good agreement was shown between the concentrations of Pt in the two fractions and the total Pt measured following digestion of the original formulation. The authors recommended this technique for quality assurance when preparing liposomal-based formulations of metallodrugs.

Concern over the level of As in *fish oil supplements* such as cod liver oil and capelin oil led Ruiz-Chancho *et al.*[128] to develop a method to screen preparations for arsenolipids by RP-HPLC-ICP-MS. Two techniques to reduce the influence of carbon on the As response were investigated; addition of CH_3OH, either *via* a post-column T-piece or directly into the spray chamber. A more constant response for different arsenolipids was better achieved with the post-column device. Examination of fish oil samples identified As-containing fatty acids, hydrocarbons and an unknown group of compounds of lower polarity.

The *British Museum has a number of bronze containers from the Roman period which contain residues believed to be medicinal preparations* including 'Punic wax', as described by Pliny. Analysis of seven samples by GC-MS, XRF and Raman spectroscopy was reported by Stacey.[129] Beeswax, fat, conifer resin, gum-derived sugars, Pb and Zn salts were identified. Likely applications of the medicines were discussed by the author.

7 Applications: foods and beverages

7.1 Progress for individual elements

7.1.1 Arsenic. A CF method to determine the bioaccessibility of *iAs and organic As* species in seafood was devised by Leufroy *et al.*[46] Powdered sample, packed into a mini-column, was leached successively with artificial saliva, then gastric and intestinal juices with the effluent flowing directly into the ICP-mass spectrometer nebuliser. Digestion of the remaining residue confirmed the mass balance of the system. Non-toxic forms were easily released using the fluids studied but iAs was poorly bioaccessible. Use of hybrid (HY) and strong anion exchange resins (SAX) was tailored to enable in-line determination of As species in water.[130] The SAX at pH < 8.0 does not retain As^{III} while a HY-hydrated Fe_xO_y resin does not retain DMA^V, allowing direct determination of these species in the effluent. The HY-AgCl resin retained all iAs allowing the effluent to be used to assess organic As. When coupled to an ICP-mass spectrometer, the LOD was 0.2 μg L^{-1} with RSDs between 3.5 and 5.1%. Another extraction method for As species in rice, wheat and fish, was reported by Raber *et al.*[131] based on a trifluoro aceticacid–H_2O_2 sample extraction. Subsequently, As^V was determined by AEC-HPLC-ICP-MS with aqueous malonic acid (5–10 mM at pH 5.6) as mobile phase. Peaks were sharp and well resolved and As^V eluted with a retention time of just 5 min.

7.1.2 Mercury. Newly synthesized magnetite nanoparticles were used for a rapid *extraction and preconcentration* of iHg at sub-ppb concentrations from water and fish samples.[39] The magnetite nanoparticles, functionalised with 1-(*p*-acetylphenyl)-3-(*o*-ethoxyphenyl)triazene iHg-binding ligands, can be isolated from the sample with a magnetic field. When coupled with ICP-AES, this extraction and system can deliver a preconcentration factor of 500 with an LOD of 0.04 ng mL^{-1} and an RSD of 2.09%. The iHg sorption capacity was 10.26 mg g^{-1} at pH 7. A sample preparation scheme involving both an ultrasonic probe at 20 kHz and an ultrasonic bath at 40 kHz was shown to be 40% better than either technique used in isolation.[35] In addition, L-cysteine was used to weaken the Hg–C bond for better extraction of MeHg. The total extraction time was only 60 s and LODs for iHg and total Hg were 0.0086 and 0.0072 μg L^{-1}, with RSDs of 2.4% and 3.1%, respectively.

7.1.3 Selenium. A non-chromatographic on-line DLLME method to effectively *preconcentrate and separate Se species* with an ionic liquid (IL) system for determination by ETAAS was devised by Martinis *et al.*[38] The IL was tetradecyl(trihexyl)phosphonium chloride (CYPHOS® IL 101) and this was used to separate the Se^{IV}–APDC complex formed; Se^{VI} was indirectly determined by prior reduction. The LOD was 15 ng L^{-1} and the RSD was 5.1% (at 0.5 mg L^{-1}). High *Mr* Se species in enriched soybean, although previously observed but uncharacterised, was identified by Chan and Caruso[132] as a Se-containing peptide, part of the Bowman-Kirk protease inhibitor sequence. A comprehensive metallomic identification of Se metabolites in enriched yeast was undertaken by Preud'homme *et al.*[50] The use of UPLC with optimised fractionation improved the identification of minor Se-containing amino acids and oligopeptides.

7.1.4 Other elements. Some of the novel applications involving *measurements of other elements* are given here while Table 2 includes references to other work. Determination of Al in Chinese processed food samples (187 samples purchased in Shenzhen) led to the realisation that high levels (up to 1126 mg kg^{-1}) were due to the additives used, and not the raw food, which presented with Al concentrations from 0.1 to 451.5 mg kg^{-1}.[133] Interferences in the determination of Cd by ID-ICP-MS have been overcome by Zhu and Chiba[41] using two chelating columns. Nobias Chelate PB-1 and, more effectively, InertSep ME-1 were used to remove nearly 100% Mo, Sn and Zr from samples at pH 7. Comparison of I speciation and bioavailability between iodized salt and chicken eggs was carried out by Lipiec *et al.*[134] A two-stage simulated digestion (pepsin followed by pancreatin) of both egg yolk and albumin was devised and I determined by SEC-ICP-MS. Yolk contained 37-times more I than the white while the bioavailability from the former was 10% and from the white it was 33%; this is in contrast to 100% availability of I^- in kitchen salt. However, the bioavailability from egg yolk decreased with cooking indicating I remains bound to non-digestible, coagulated and insoluble proteins. Several other analytical methods for the determination of I were

Table 2 Foods and beverages (for column 3, L = liquid, S = solid, Sl = slurry)

Element	Matrix	Technique; atomisation; presentation	Sample treatment/comments	Ref.
Al	Wheat flour	AA; ETA; L	Samples were digested in a mixture of HNO_3 and H_2O_2 in closed PTFE vessels. A $Mg(NO_3)_2$ solution 1 g L^{-1} was used as the matrix modifier. The RSDs obtained ranged from 1.7% to 2.4%, and recoveries were reported in the range 98 to 102%	33
Al	Food and food additives	MS; ICP; L	A survey of the Al content of processed foods, raw material and food additives in China (178 samples). High levels of Al were reported for some processed foods (up to 1226 mg kg^{-1}) and food additives (0.005–57.4 g kg^{-1}) but Al was found to be lower in the raw materials (0.10–451.5 mg kg^{-1})	133
As	Foodstuffs (vegetables, crops)	AA; FI-HG; L;	Contaminated foodstuffs and groundwater were collected and analysed using a FI-HG method to estimate total As content. The As levels in boro and aman rice were reported with mean values of 194 and 156 μg kg^{-1} respectively	107
As	Rice-based infant foods	MS; ICP; L MS; ICP; HPLC	Gluten-free rice, cereals with gluten, and puréed baby foods from Spain, UK, China and the USA were analysed for total and iAs, the latter using prior chromatographic separation. It was reported that all rice-based products contained high levels of iAs with values greater than 60% of the total As content	149
As	Rice and infant cereal products	MS; ICP; HPLC	Extraction of the As species (iAs, MMA, and DMA) was performed using 0.2% HNO_3 and 1% H_2O_2. Results for the analysis of 29 samples were reported and total As found was in the range 1 to 324 μg kg^{-1}. The CRMs from the NMIJ; 7503a, NCS ZC73008, and NIST; SRM 1568a, were used to assess method bias	181
As	Organic brown rice syrup	MS; ICP; IC	Method for determination of total As and As species using IC separation prior to detection. Samples were found to contain iAs and DMA	148
As	Rice wheat and tuna fish	MS; ICP; HPLC	Samples were extracted with trifluoroacetic acid–H_2O_2 and arsenate separated by anion-exchange HPLC using 10 mM malonic acid at pH 5.6 as mobile phase prior to detection. The LOD was reported as 0.05 μg As L^{-1} (for 20 μL injection) or1 μg As kg^{-1} in dry sample	131
As	Seafood	MS; ICP; HPLC	Total As content, in seafood samples and dialyzable and non-dialyzable fractions, was determined after a microwave-assisted acid digestion treatment. As species were determined following an optimised matrix solid phase dispersion and separation by HPLC. The accuracy of the procedure was assessed for total As using DORM-2 and BCR-627 CRMs	152
As	Seafood	MS; ICP; L	Continuous-flow on-line digestion by pumping artificial saliva, gastric and intestinal juices through a mini-column of powdered sample; the leachates were supplied to the ICP directly for determination of bio-available total As and *via* an anion exchange column for detection of As species	46
As	Fish oils (cod liver oil and capelin oil)	MS; ICP; L	A method for screening lipid-soluble As compounds in fish oils by RP-HPLC using a gradient elution with CH_3CH_2OH and CH_3COO^- buffer at pH 6. The addition of MeOH post-column through a T-piece maintained constant response for several As-containing lipids covering a wide range of polarities. Reported LODs were in the range 5–11 μg As L^{-1}	128
As	Drinking water	MS; ICP; L, AA; HG; L	Evaluation of strong base anion exchange and hybrid resins for the separation and subsequent determination of iAs and organic As species. The LOD for the ICP-MS method was given as 0.2 μg L^{-1} and the RSD of all As species investigated was reported in the range 3.5 to 5.1%	130
B	Drinking water	AE; ICP; L	The level of B in Chilean public tap water was determined directly and reported in the range 0.22 to 11.3 mg L^{-1}, with a median value of 2.9 mg L^{-1}. The concentrations of B found in bottled water samples were in the range 0.01 to 12.2 mg L^{-1} The levels of B reported were higher than WHO recommended limits	113
Bi	Water	AA; F; L	Ion-pair dispersive LLME was used to preconcentrate Bi by injecting 2-(5-bromo-2-pyridylazo)-5-(diethyl amino) phenol reagent as complexing agent and 700 μL of $(CH_3)_2CO$ (dispersing solvent) containing 75 μL of dichlorobenzene (extracting solvent) into 10 mL of aqueous solution. An enrichment factor of 28.6 was achieved. An LOD of 3.0 ng mL^{-1} was reported and the RSD for the method was given as1.5%	111

Table 2 (*Contd.*)

Element	Matrix	Technique; atomisation; presentation	Sample treatment/comments	Ref.
Cd	Food	MS; ICP; L	A sample pre-treatment method was developed to eliminate spectral interferences. An aliquot of 0.6 mL of NH_4OH was added to 10 mL of pre-digested sample (in 0.3 M HNO_3) which was then loaded into a syringe-driven SPE chelating column at a flow rate of 5 mL min^{-1}. The column was washed with H_2O prior to elution of Cd with 2 mL of 0.3 M HNO_3. An ID-based procedure was used for analysis and was validated using NMIJ CRMs	41
Cr	Black, green and herbal teas	AA; ETA; L	Samples soaked in boiled H_2O (200 mL) were treated with 0.1 M Na_2CO_3 to measure total Cr^{VI} and microwave acid digestion was used to prepare samples for total Cr determination. Total Cr^{VI} was reported in the range 0.03 and 3.15 μg g^{-1} for black tea and between 0.03 and 0.14 μg g^{-1} for green tea, but below the LOD for herbal tea	157
Cr	Plant-derived foodstuffs	AA; ETA; Sl	Samples were prepared as slurries and 10 μg Nb was added as permanent modifier. The LOD for the method was given as 86.6 ng g^{-1} for a 0.75% (w/v) slurry concentration. The RSDs were reported to be <10%. Recoveries for Cr in CRMs were in the range 95 to 103%	182
Cr	Drinking water	AA; F; L	Speciation by adsorption of Cr^{VI} oxyanions on a Ni–Al layered double hydroxide nano-sorbent at pH 6.0. The determination of total Cr, and indirectly Cr^{III}, was subsequently achieved by pre-oxidation of Cr^{III} to Cr^{VI} using H_2O_2. The LOD for Cr^{VI} was reported as 0.51 ng mL^{-1}	80
F	Tea	Molecular absorption; ETV; L	Tea samples were prepared using acid digestion, alkaline solubilization and conventional aqueous infusion. The determination of F as CaF was achieved by molecular absorption spectrometry. The LOD was reported as 0.16 mg L^{-1}. The concentration of F found in the 10 solid samples analysed ranged from 42 μg g^{-1} to 87 μg g^{-1}	61
Fe	Baby food	AA; F; Sl	Samples were dried overnight at 105 °C and ground in an agate mortar. A 500 mg sub sample was slurried in 20 mL of 0.05% Triton X-114 containing 0.1 M HNO_3 and homogenised for 5 min before direct analysis of the suspension. The reported LOD was 5.5 μg g^{-1} and the bias of the method was assessed using CRMs	183
Hg	Seafood (squid, penaeus and ling fish)	AF; CV; L	The iHg and total Hg in fish samples were completely extracted ultrasonically in 60 s. L-Cysteine was used to weaken the Me–Hg bond. LODs for iHg and total Hg in aqueous solutions were 0.0086 μg L^{-1} and 0.0072 μg L^{-1}, respectively. The RSDs for 11 replicate determinations of 1 μg L^{-1} Hg were 2.4% for inorganic Hg and 3.1% for total Hg. The accuracy of the method was verified using CRMs	35
Hg	Seafood	MS; ICP; L, MS; EI; L	A review of species specific ID and species non-specific ID methods for the determination of Hg species in seafood	14
Hg	Fish CRMs: tuna fish (CE-464), lobster hepatopancreas (TORT-2) and dogfish (DOLT-2)	AA; ETA; S	Direct solid sampling method for total Hg used Ir film and 5 μg Pd + 3 μg Mg solution as permanent and co-injected chemical modifiers. For direct chemical speciation (Hg^{2+} and MeHg by difference from total Hg), 5 μg Pd + 3 μg Mg + 0.5% w/v Triton X-100 co-injected modifiers were employed. Three CRMs were used to verify the accuracy of the method	153
Hg	Dogfish muscle (DORM-2)	AF; CV; L	Chromatographic speciation of iHg, MeHg and EtHg on an RP C_{18} monolithic column using a multi-isocratic elution with 0.005% 2-mercapthoethanol in 240 mM NH_4CH_3COO (pH 6)–CH_3CN (99 : 1, v/v), followed by 0.005% 2-mercapthoethanol in 240 mM NH_4CH_3COO (pH 6)–CH_3CN (90 : 10, v/v). The eluted Hg species were oxidized under post-column UV radiation and reduced using $SnCl_2$ in an acidic medium prior to detection	118
Hg	Water and Fish	AE; ICP; L	Modified Fe_3O_4 magnetite nanoparticles functionalized with triazene groups were used to extract and preconcentrate Hg from water and fish samples using an externally applied magnetic field. It was reported that the LOD for the method was 0.04 ng mL^{-1} and the RSD was 2.09% for five replicate extractions and measurements of 10 μg of Hg^{2+} in 1000 mL of liquid sample	39
Hg	South American Red wines	MS; ICP; FI-CV MS; ICP; GC	Hg species were derivatised for GC using a 1% (m/v) $NaBPh_4$ solution, followed by extraction of Hg species for analysis. Recoveries were reported in the range 99% to 104% for Hg^{II} and MeHg. The LODs for Hg^{II} and MeHg were 0.77 and 0.80 μg L^{-1}, respectively	65

Table 2 (*Contd.*)

Element	Matrix	Technique; atomisation; presentation	Sample treatment/comments	Ref.
I	Foods and dietary supplements	MS; ICP; L	Samples were digested in KOH in an oven or open microwave vessel. The LOQ reported for the method was 25–50 μg kg^{-1}. The RSDs were on average 2.3% for the analysis of a milk powder RM and 4.3% for the analysis of a dietary supplement tablet RM. Results were reported as 100% and 94.2% of certified values respectively	135
I	Foods and diets	MS; ICP; L	Samples were prepared using TMAH alkaline digestion. The accuracy of the method was assessed by the analysis of NIST SRM 1549 non fat milk. It was reported that the I content in foodstuffs analysed using the method ranged from <0.02 to 0.101 mg kg^{-1} for cereals, 87 to 299 μg kg^{-1} for milk, and 86 to 271 μg kg^{-1} for cheese products	136
I	Infant formula and adult nutritional products	MS; ICP: L	All samples were treated with HNO_3 using closed vessel microwave digestion and NH_4OH solution was then added to the samples to prevent loss of I.The LOD reported for the method was 0.3 ng mL^{-1} as total I. Results were obtained within certified limits for two NIST SRMs using the method	137
I	Milk	MS; ICP; L	135 samples of cow's milk were analysed after digestion with TMAH. It was noted that there were no significant changes to I content of cow's milk over a 5 year period. A mean level of 122.0 ± 36.8 μg L^{-1} I was reported in the samples	145
I	Chicken eggs	MS; ICP; SEC	Egg samples were treated with buffer (Tris HCl, pH = 7.5) and enzymatic extraction media in a two-stage digestion model simulating gastric (pepsin digestion) and intestinal (pancreatin digestion) juices, to assess *in vitro* bioavailability of I species	134
Li	Mineral water	XRF; —; L	Li was precipitated with iron to yield a stoichiometric potassium lithium periodatoferrate complex which was dissolved and pipetted onto Mylar foil for XRF analysis. It was reported that Li could be determined at levels as low as 1 μg using the method	72
Mn	Drinking water	AA; F; L	See Cr, ref. 80. The determination of total Mn, and indirectly Mn^{II}, was subsequently achieved by pre-oxidation of Mn^{II} to Mn^{VII}using KIO_4. The LOD for Mn^{VII} was reported as 0.47 ng mL^{-1}	80
P	Fish diets	AA; ETA; L	Dry samples (100 mg minimum) were acid digested in a domestic microwave system using Parr Teflon bombs at high pressure. A 1000 μg mL^{-1} La solution was used as chemical modifier in the ETA. The LOD reported was 0.15 mg P g^{-1} of dry sample	59
Se	Se-enriched Cabbage	MS; ICP; HPLC	Soluble Se compounds were extracted from parts of cabbage with protease XIV. Se species were separated in the enzymatic extracts using ion exchange HPLC. The total Se found in cabbage leaves was 4.80 ± 0.25 μg Se g^{-1} and in red cabbage 0.96 ± 0.04 μg Se g^{-1}	150
Se	Se-enriched Soybean	MS; ICP; HPLC	Multi-technique characterisation (including HPLC-ICP-MS and HPLC-Chip-ESI-ion trap-MS) of Se-containing proteins in soybeans	132
Se	Garlic	AA; ETA; L	An on-line ionic liquid dispersive micro-extraction system was used to selectively separate Se^{IV} by forming a Se–APDC complex followed by extraction with CYPHOS ® IL 101. An LOD of 15 ng L^{-1} was reported with an RSD for 10 replicate measurements of 5.1% for 0.5 μg L^{-1} Se	38
Se	Turkey meat	ICP; MS:L ICP; MS:HPLC	In a study of the effect of diet supplements containing additions of Se-enriched yeast or Na_2SeO_3, the tissues of female turkeys on such diets were analysed for total Se, SeMet and SeCys	154
V	Foodstuffs (wine, tea, tomatoes)	AA; ETA; L	A ternary complex formed between V, 2-(2′-thiazolylazo)-*p*-cresol, and ascorbic acid, was subsequently extracted using Triton X-100, for preconcentration of V. The LOD was reported as 0.05 ng mL^{-1} V and the RSD for the method was given as 3.9%	138
Zn	Baby food	AA; F;S	See Fe, ref. 183. The reported LOD for Zn was 3.4 μg g^{-1}	183
Various (4)	Second French Total Diet Study	AA; F; L	Foodstuffs (1319 types) that comprise the French total diet were analysed for Ca, K, Mg and Na. Samples were prepared using microwave-assisted digestion and introduced to the flame *via* a micro-sampling procedure. Results were compared with those from the First French Total Diet Study	141
Various (9)	Second French Total Diet Study	MS; ICP; L	Samples (1319) originating from the French Total Diet Study were subjected to microwave-assisted digestion and analysed for Ag, Ba, Fe, Ga, Ge, Sn, Sr, Te and V. The food groups containing the highest levels for these elements were reported	142

Table 2 (*Contd.*)

Element	Matrix	Technique; atomisation; presentation	Sample treatment/comments	Ref.
Various (9)	Second French Total Diet Study	MS; ICP; L	Samples were prepared using microwave-assisted digestion prior to determination of Co, Cr, Cu, Li, Mn, Mo, Ni, Se and Zn. The food products containing some of the highest levels of these essential elements included tofu, fish and shellfish, confectionery and ice cream	140
Various (7)	Foodstuffs	MS; ICP; L	Optimisation of collision cell conditions to remove spectral interferences for determination of trace elements (As, Cr, Co, Fe, Ni, Se and V) in foods	47
Various (19)	Infant formula	MS; ICP; L	Samples were digested in HNO_3 using a microwave-assisted procedure and CH_3COOH was added to sample solutions and to standards prior to the determination of 19 elements. Recoveries were reported in the range 95–108% and RSDs for the method were between 0.3 and 4.2%. Good agreement with NIST SRM values was obtained	184
Various (3)	Infant formula and adult nutritional products	MS; ICP; L	Samples were digested using a closed vessel microwave oven system incorporating internal standards (Ni and Te). The LOQs for Cr, Mo and Se were reported as 0.4, 0.2, and 0.4 ng mL^{-1}, respectively. The accuracy of the method was assessed using NIST SRMs	185
Various (10)	Milk	AA; ETA; L	A W permanent modifier with co-injection of $Pd(NO_3)_2$ and W-Ru permanent modifiers was used for the simultaneous direct determination of As, Bi, Co, Cr, Cu, Fe, Mn, Pb, Sb, and Se in milk. An air-assisted pyrolysis step was used to remove organic matter. Results for the analysis of 14 commercial milk samples were reported	186
Various (4)	Milk powder	AE; ICP; L and LA LIBS	Laser sampling techniques for the direct determination of Ca, Mg, Na and Zn were compared. Accuracy was reported to be affected by matrix effects and bias in the range 1–60% was reported for the methods	64
Various (20)	Soy and dairy yoghurts	MS; ICP; L	Samples were microwave digested prior to analysis. Both Cu and Mn were found at elevated levels (up to 30 fold) in soybean products in comparison with dairy yoghurts and Ni at concentrations up to 450 ng g^{-1} in some samples	146
Various (10)	Dairy products and meat	MS; ICP; L	Mineral (Ca, K, Mg, Na, and P) and trace element (Cu, Fe, Hg, Se and Zn) levels were measured in Icelandic whole milk, fresh cheese (skyr), firm cheese (Gouda), lamb meat and minced beef, skimmed milk, cream and whey. Seasonal and geographical variation of Se in milk was reported. The Se content in meat was also found to be variable; Hg was reported as below the LOD of 0.3 μg per 100 g except for one sample of cheese	139
Various (4)	Fresh and Processed Meat	AA; F; L AA; ETA; L	Samples were treated with TMAH prior to determination of Ca, Cu, Fe and Mg. The LODs reported were 45, 0.2, 16 and 0.3 μg g^{-1}, respectively	156
Various	Green tea	Various	Certification and reference values were reported for three new issue NIST green tea-containing reference materials; SRM 3254 *Camellia sinensis* (green tea) leaves, SRM 3255 *Camellia sinensis* (green tea) extract and SRM 3256 green tea-containing solid oral dosage form	22
Various (37)	Tea leaves (NMIJ CRM 7505a)	MS; ICP; L, AE; ICP; L, AA; ETA; L, AA; F; L	In the characterisation of an NMIJ developed CRM for trace element content, property values were reported for 19 elements and informative values for 18 elements including all of the lanthanides, except for Pm	21
Various (18)	Vegetables (tomato, cabbage, pepper, and parsnip)	PIXE; —; L	Samples were chemically mineralised and the resulting solution deposited onto Mylar foil targets with Y added as internal standard. The method was applied to the determination of 18 elements in SRMs	151
Various (6)	Tomato paste	MS; ICP; L	The method was validated using NIST SRM 1573a (tomato leaves) with relative errors reported in the range 1.4% to 9.0%. Tomato paste samples gathered from the supermarkets in Turkey were analysed using the validated method for Cd, Cu, Fe, Pb, Sn and Zn and results were compared with literature values	187
Various (16)	Spinach leaves (CRMs NIST 1570a) Dogfish muscle (DORM-2) and lobster hepatopancreas (TORT-2)	AE; ICP; L and HG	Evaluation of a dual nebulisation system for the simultaneous determination of hydride forming and non-hydride forming elements. The LODs were reported in the range 0.002 to 0.0026 μg mL^{-1} for the hydride forming elements and between 0.0034 and 0.0121 μg mL^{-1} for the non-hydride forming elements; elemental recoveries were in the range 97 to 103%	63

Table 2 (*Contd.*)

Element	Matrix	Technique; atomisation; presentation	Sample treatment/comments	Ref.
Various	Fish (tilapia tissues)	MS; ICP; L	Evaluation of experimental design applied to method development for microwave-assisted digestion of samples (in 2.5 mL HNO_3, 0.5 mL HCl and 7.0 mL H_2O) for multielement determinations. Agreement was obtained with certified values for the analysis of DORM-3, DOLT-4 and ECM-CE278 RMs	32
Various (18)	Wheat flour	MS; ICP; L	The method was applied to commercially available conventional and organic wheat flour samples	147
Various (20)	Bread	MS; ICP; L	Concentrations of 20 minor, trace and ultra trace elements relevant to human health were determined in three varieties of Lebanese bread sampled at five geographical locations	188
Various (14)	Red wine	MS; ICP; L	Ultrasound sample preparation was used prior to determination of lanthanides using FI. LODs were reported in the range 0.24 to 10.8 ng L^{-1}	45
Various (56)	Red wine	MS; ICP; L, AE; ICP; L	A total of 56 elements were determined in 1397 samples of Australian wine. The use of element composition to discriminate between wines grown in different geographical regions was examined	158

proposed by Sullivan and Zywicki,[135] Tinggi *et al.*[136] and Pacquette *et al.*[137] Preconcentration of V from tea, tomatoes and wine by CPE was optimised using 2-(2′-thiazolylazo)-*p*-cresol and ascorbic acid to form the ternary complex.[138]

7.2 Single and multielement applications in food and beverages

7.2.1 Dietary intake studies. The never-ending issues of As contamination in regions of the Indian subcontinent continue to motivate research in understanding *dietary intakes* of toxic elements. Samal *et al.*[107] investigated As in drinking water and foodstuffs in the Nadia region of West Bengal using FI-HG-AAS. Total intake from foodstuffs, represented by boro and aman rice (mean As content 780 and 674 μg kg^{-1}, respectively), was calculated at 560 μg per day (adults) and 393 μg per day (children) with 50–60% retention observed *via* urine analysis. The I nutritional status in young children from Australia was assessed by Tinggi *et al.*,[136] analysing food by alkaline TMAH digestion followed by ICP-MS. The mean daily intake was very variable at 93.1 ± 76.7 μg per day (range: 36.9–288.1 μg per day). The Icelandic diet was studied by Reykdal *et al.*[139] for seasonal and geographical variations in 10 selected mineral and trace elements using ICP-MS. Variations in Se concentrations were only found in whole milk whilst concentrations in beef were deemed to be variable and low (1.4–9.6 μg 100 g^{-1} w/w). Results from the 2nd French Total Diet Study continue to be reported episodically by Guerin's team.[140–142] The food groups with the highest levels ('sweeteners, honey and confectionery' and 'fish products') were the same as those reported last year.

7.2.2 Human milk and infant formula. The nutritional suitability of human milk produced by mothers of preterm infants in terms of Cu, Mn, Se and Zn was studied where infants were born <34 weeks or with a body weight <1.8 kg.[143] Although Mn exceeded daily requirements suggested by the American Academy of Paediatrics and Cu was below, both concentrations increased the closer the birth was to term. Concentrations of Se and Zn met daily requirements regardless of length of the pre-term period. Measurements were by AAS. Exposure to Ce through industrial products or nuclear fission was thought to be of concern, motivating a biomonitoring programme with paired samples of milk and serum from Munich (Germany) and Madrid (Spain), using ICP-MS.[121] The median concentration of Ce in *human milk* was 13 ng L^{-1} across both regions, however blood serum concentrations were around the LOQ of 10 ng L^{-1} in Munich and, in Madrid, it ranged from 21.6 to 70.3 ng L^{-1}. These data suggest there is no increased risk to nursing neonates since no trans-mammary enrichment was observed. The association between lifestyle and heavy metal content (Cd, Hg, Pb) in human milk, measured by AAS, was explored by Garcia-Esquinas *et al.*[144] in samples collected three weeks postpartum from mothers in Madrid (Spain). Unsurprisingly, smoking and exposure to motor vehicle traffic were shown to increase levels in Cd and Pb, respectively (geometric means: 1.31 μg L^{-1} and 15.56 μg L^{-1}). Older women and those previously having given birth presented lower concentrations of Hg (general geometric mean: 0.53 μg L^{-1}) which the authors ascribe to a clearance mechanism over a person's lifetime.

7.2.3 Milk and dairy products. The I status of *cow's milk* in Thuringia (Germany) was monitored over a period of 5 years (2007–2011) and compared with that of human milk from mothers living in the same region.[145] Samples were digested with TMAH and I determined by ICP-MS. The mean I concentration over the five years was 122.0 ± 36.8 μg L^{-1} with organically produced milk containing on average 51 μg L^{-1} less I ($P < 0.001$). Human milk showed a slightly higher I concentration of 170 ± 96 μg L^{-1} but with larger variation among individuals. Dairy and soy yogurts were compared for micronutrient value and toxic element status after development of a suitably validated ICP-MS method.[146] Soy products were found

to contain much higher levels of Cu and Mn (up to 30-fold higher) while Ni was also higher in soy yogurt with maximum concentrations recorded at 450 ng g^{-1}.

7.2.4 Cereals, flour and rice. As constituents of staple diets the *trace element and mineral contents of cereals, flour and rice* are particularly important. A comparison of organically and conventionally produced wheat flours was undertaken using an optimised and validated multi-element ICP-MS method.[147] Significant differences between the two agricultural practices were found with concentrations of Cr, Mg, Mo, Ni and V being higher in organic samples while those of conventional wheat flour were higher in Al, As, Cd and Pb. Organic brown rice syrup (OBRS) can be used as a substitute for high fructose corn syrup, as a sweetener for food products. As rice may contain unreasonable levels of iAs it was suggested by Jackson *et al.*[148] that OBRS and finished foodstuffs could contain inappropriate concentrations of As. Samples of toddler milk formulae, cereal bars and high-energy foods were analysed by ICP-MS and IC-ICP-MS and all contained higher As concentrations than were seen in products that did not include OBRS. Most of the As was present as iAs with some MMA. Organic milk formulae had up to six times more total As than the US EPA safe drinking water limit. Total As and iAs determination in infant rice from China, Spain, UK and USA was undertaken using ICP-MS and HPLC-ICP-MS;[149] gluten-based cereals and puréed baby foods from Spain were also analysed. The iAs content of rice samples was significantly higher than gluten-containing cereal and represented over 60% of total As with the balance being DMA. The Chinese limit of 150 μg kg^{-1} was not exceeded by 77% of samples although when expressed as body weight of infants aged 8–12 months, iAs was higher than the predicted adult exposure from drinking water.

7.2.5 Vegetables, fruits and nuts. The binding of Cd to vegetable proteins was studied in Cd-exposed spinach using LA-ICP-MS after protein separation by PAGE and electroblotting onto membranes.[78] The Cd-bound protein was investigated by FT-ICR and identified as ribulose-1,5-bisphosphate carboxylase/oxygenase (RUBISCO). The authors then went on to prove RUBISCO binds to Cd as well as to Cu^{II}, Fe^{II} and Mn^{II}.

The spatial distribution of Se species in white and red cabbage that had been sprayed twice with solutions containing Se^{VI} at concentrations of 20 mg L^{-1} and 0.5 mg L^{-1}, respectively, was determined by Mechora *et al.*[150] using HPLC-ICP-MS. The total Se concentrations, the soluble concentrations and the percentages of the latter present as SeMet, were measured in root, stem and leaves. For white cabbage, SeMet represented 94% of the soluble Se from the roots (55% for red cabbage) while only 23% was found in the soluble Se from leaves and stems. This was in contrast to red cabbage where SeMet was 80% and 41% of the soluble Se for leaves and stems, respectively.

Analysis by PIXE of four *types of vegetable* grown in Romania was carried out by Pantelica *et al.*[151] Samples were digested and thin targets prepared by pipetting solutions onto Mylar foils. This allowed determination of elemental concentrations (Al, As, Br, Ca, Cl, Cr, Cu, Fe, K, Mn, Ni, Pb, Rb, S, Se, Sr, Ti and Zn) without corrections for X-ray self-absorption and proton stopping in target, necessary when using thick target preparation.

7.2.6 Fish and seafood. *In vitro* simulated gastric and intestinal digestion/dialysis has again been used by Bermejo-Barrera[152] to assess the bioavailability of various As species (As^{III}, As^{V}, AB, AC, DMA and MMA) in raw seafood using ICP-MS and matrix solid phase dispersion. Dialysability was found to be high (84.6–10%) for total As and species. Bioavailability was negatively correlated with fat content although no correlation was observed with protein content. Two simple and fast ETAAS methods were proposed for the *analysis of fish*: one, for the optimised and validated determination of total Hg, iHg and MeHg in fish by Naozuka and Nomura,[153] the other for the determination of P with minimal sample amounts (100 mg dw) as an alternative to colorimetric methods.[59] Solid sampling ETAAS with a mixed Pd–Mg chemical modifier (5 μg Pd + 3 μg Mg) was used for Hg speciation while an Ir film was used in addition for total Hg. After microwave-assisted acid digestion, P was determined at a wavelength of 213.6 nm with D_2 background correction and with a La chemical modifier (1000 μg mL^{-1} La solution). Optimal pyrolysis and atomisation temperatures were 1600 and 2700 °C and spiked recovery was 94% ± 11% ($n = 3$) with an LOD of 0.15 mg g^{-1} dw.

7.2.7 Meat and poultry. The content of SeMet, SeCys and total Se in turkey meat was assessed using HPLC-ICP-MS by Juniper *et al.*[154] after dietary supplementation for 84 days with selenized yeast (SY) or sodium selenite at two levels (low: 0.3 mg kg^{-1} and high 0.45 mg kg^{-1}; control 0.2 mg kg^{-1}). There were significant differences between both types and levels of supplementation, although accumulation was highest in birds fed SY. Visceral tissues contained predominantly SeCys whereas breast meat comprised mainly SeMet. Thigh meat also contained more SeCys than SeMet. Alligator (*A. mississippiensis*) meat and bone were analysed by ICP-AES.[155] Concentrations of Cd and Pb were below the LOD of 0.5 μg g^{-1} and the measured concentrations of Cu, Fe and Zn were not considered potentially toxic. A simple method for sample preparation using TMAH was proposed for the determination of Ca, Fe and Mg in *fresh and processed meat* using FAAS and ETAAS for Cu.[156] No spectral interferences were found for Cu determination following investigations with HR-CS-AAS.

7.2.8 Drinking water and non-alcoholic beverages. Safe levels of B in *drinking water* are still open for question and work by Cortes *et al.*[113] highlighted issues in northern Chile, an area naturally high in this element. This study represented the first detailed assessment of B exposure in Chilean tap and bottled water (173 samples) analysed by ICP-AES, along with urine provided by volunteers (22 samples) over four years. Boron concentrations in bottled water samples ranged from 0.01 to 12.2 mg L^{-1} while the median value for tap water was 2.9 mg L^{-1} (range 0.22–11.3 mg L^{-1}). Urinary B concentrations (0.45–17.4 mg L^{-1}, median 4.28 mg L^{-1}) were shown to be correlated with the volunteers' tap water consumption of B ($r = 0.64$). An indirect XRF determination of Li in mineral water, mediated by Fe precipitation with $KLiFeIO_6$ complex, was discussed by Zawisza and Sitko.[72] The solution containing the complex was pipetted onto a Mylar film allowing as little as 1 μg to be

determined. Mineral water samples collected from therapeutic sources contained between 3.3 and 12.5 ppm which the authors situate higher than tap water but much less than medical doses. A method for the speciation of Cr and Mn by FAAS was proposed using a Ni–Al layered double hydroxide as SPE nano-sorbent.[80] At pH 6, adsorption of Cr^{VI} and Mn^{VII} oxyanions onto the sorbent occurred with the lower valence ions passing through unretained. Total concentrations were determined after oxidation with H_2O_2 and KIO_4. After optimisation, the Cr^{VI} and Mn^{VII} LODs were measured as 0.51 and 0.47 ng mL^{-1}, respectively.

Mandiwana *et al.*[157] used ETAAS to *analyse different teas* and showed that up to 20% of total Cr was present as Cr^{VI} in black compared to 14% in green tea with none detected in herbal tea. Total concentrations were measured following acid digestion while Na_2CO_3 was used to extract Cr^{VI}. Average total Cr concentrations were 0.70 ± 0.29 μg g^{-1} in green tea, 0.95 ± 0.27 μg g^{-1} in herbal tea with black tea having the highest average concentration of 4.38 ± 4.23 μg g^{-1}. The maximum concentration of Cr^{VI} in black tea was 3.15 μg g^{-1}. Determination of F in teas was carried out by Mores *et al.*[61] using the 606.44 nm molecular absorption band of CaF in the graphite atomiser of an HR-CS-AAS spectrometer. An LOD of 1.6 ng was obtained with a linear range up to 25 mg L^{-1}. Total F for 10 samples was determined between 42 and 87 μg g^{-1} with extraction rates from 48% to 74%.

7.2.9 Alcoholic beverages. Mercury speciation (iHg, MeHg) in red wine was carried out using GC-ICP-MS with $NaBPh_4$ derivatisation (1% m/v) and FI-CV-ICP-MS for total Hg.[65] The authors reported only total Hg concentrations in samples from South America as other species were below their respective LODs. Total Hg reached a maximum of 0.55 ± 0.02 μg L^{-1}. The determination of the lanthanide series *elements in wine* is often undertaken out for authenticity purposes, although it is problematic. Bentlin *et al.*[45] indicated that the use of an ultrasonic probe for 90 s with a 10-fold dilution gave best results in sample preparation for determination by ICP-MS. Lanthanide concentration data allowed discrimination of red wines from three countries from South America. An impressive set of analytical data from nearly 1400 Australian wine samples and 56 elements determined by ICP-MS and ICP-AES was published by Martin *et al.*[158] Wine growing regions from within the same state were easily discriminated with LDA with the exception of South Australia where several geographical indications are situated in close proximity.

Abbreviations

2D	Two-dimensional
3D	Three-dimensional
5-Br-PADAP	2-(5-Bromo-2-pyridylazo)-5-(diethyl amino) phenol
AA	Atomic absorption
AAS	Atomic absorption spectometry
AB	Arsenobetaine
AC	Aedenocholine
AEC	Anion exchange chromatography
AF	Atomic fluorescence
AFM	Atomic force microscopy
AFS	Atomic fluorescence spectrometry
APDC	Ammonium pyrrolidinedithiocarbamate
ASU	Atomic Spectrometry Update
CDC	Centers for Disease Control and Prevention
CE	Capillary electrophoresis
CF	Continuous flow
CPE	Cloud point extraction
CRM	Certified reference material
CT	Computer tomography
CV	Cold vapour
DDC	Diethyldithiocarbamate
DLLME	Dispersive liquid–liquid microextraction
DMA	Dimethylarsenic
DNA	Deoxyribonucleic acid
DRC	Dynamic reaction cell
EDXRF	Energy dispersive X-ray diffraction
EDTA	Ethylenediamine tetraacetic acid
EPA	Environmental Protection Agency
EPO	Erythropoietin
ES	Electrospray
ESI	Electrospray ionization
$ESI\text{-}MS^n$	ESI-MS with two or more (n) detectors
ETAAS	Electrothermal atomic absorption spectrometry
EtHg	Ethylmercury
ETV	Electrothermal vaporization
FAAS	Flame atomic absorption spectrometry
FI	Flow injection
FT	Fourier transform
FT-ICR	Fourier transform ion cyclotron resonance
GC	Gas chromatography
HDL	High density lipoprotein
HG	Hydride generation
HPLC	High performance liquid chromatography
HR	High resolution
HR-CS-ETA	High resolution continuum source atomic absorption spectrometry
HR-ICP-MS	High resolution inductively coupled plasma mass spectrometry
iAs	Inorganic arsenic
IC	Ion chromatography
ICP-AES	Inductively coupled plasma atomic emission spectrometry
ICP-MS	Inductively coupled plasma mass spectrometry
ID	Isotope dilution
iHg	Inorganic mercury
IL	Ionic liquid
IUPAC	International Union of Pure and Applied Chemistry
JAAS	Journal of analytical atomic spectometry
LA	Laser ablation
LC	Liquid chromatography
LIBS	Laser induced breakdown spectroscopy
LLME	Liquid–liquid–liquid microextraction
LOD	Limit of detection
LOQ	Limit of quantification
MALDI	Matrix-assisted laser desorption ionization
MC-ICP-MS	Matrix-assisted laser desorption ionization
MeHg	Methyl mercury
MeOH	Methanol

MMA	Monomethylarsenic
MRI	Magnetic resonance imaging
MS	Mass spectrometry
NIST	National Institute of Standards and Technology
NMIJ	National Metrological Institute of Japan
OBRS	Organic brown rice syrup
PAGE	Polyacrylamide gel electrophoresis
PCA	Principal component analysis
*p*HMB	*p*-Hydroxy-mercuribenzoic acid
PIGE	Particle-induced gamma ray emission
PIXE	Particle-induced X-ray emission
ppb	Parts per billion (10^{-9})
ppm	Parts per million (10^{-6})
ppt	Parts per trillion (10^{-12})
PTFE	Poly(tetrafluoroethylene)
PFA	Perfluoroalkyloxy
Q-	Quadrupole
RBS	Rutherford backscattering spectrometry
REE	Rare earth element
RM	Reference material
RP	Reversed phase
RSD	Relative standard deviation
SAX	Strong anion exchange
SEC	Size exclusion chromatography
SeCys	Selenocysteine
SeMet	Selenomethionein
SF	Sector field
SIMS	Secondary ion mass spectrometry
SPE	Solid phase extraction
SRM	Standard reference material
SR-XRF	Synchrotron radiation X-ray fluorescence
TEM	Transmission electron microscopy
TMAH	Tetramethylammonium hydroxide
TOF	Time-of-flight
TXRF	Total reflection X-ray fluorescence
UPLC	Ultra performance liquid chromatography
UV	Ultraviolet
WHO	World Health Organisation
XRF	X-ray fluorescence
XRFM	X-ray fluorescence microscopy

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