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Atomic Spectrometry Update: review of advances in the analysis of clinical and biological materials, foods and beverages

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This review covers publications from the second half of 2016 to the middle of 2017. Techniques and applications relevant to clinical and biological materials, foods and beverages are discussed in the text, presenting the key aspects of the work referenced, while the tables provide a summary of the publications considered. Further to the observations made in the 2017 Update, we have noted the increase in publications featuring nanomaterials. Topics relate to exposure and absorption of nanoparticles; potential toxicity, use as reagents in

analytical methods and the analysis or characterisation of these materials. A growing number of techniques are being applied to bio-imaging. In particular, those involving XRF spectrometry are being applied to a large range of biological sample types. A gradual trend during recent years, that is now quite apparent, has been the increasing proportion of publications that involve foods and beverages compared with clinical samples. Not necessarily related, but another trend is the growing number of reports from laboratories in the Republic of China.

1 Reviews

This latest Update adds to that from last year[1] and complements other reviews of analytical techniques in the series of Atomic Spectrometry Updates, also from the previous year.[2–6]

Sample preparation is crucial to all analytical procedures and features extensively in all our Updates. Much of the recent interest has focused on dispersive liquid–liquid microextraction (DLLME). Campillo *et al.*[7] produced a review of the different variations and examples of the technique that have developed during the last ten years. With a more specific objective, de la Calle *et al.*[8] discussed how DLLME may be coupled with ETAAS, and the applications made possible when using this approach.

In our recent reviews we have drawn attention to the technical developments and the varied applications associated with *bio-imaging techniques*. As a consequence, a number of review articles featuring different aspects of imaging, were published in the last year. Collingwood and Adams[9] prepared a tutorial review on X-ray methods applied to imaging analysis of the brain. Methods covered included XRF spectrometry for elemental imaging, XRA spectrometry for speciation imaging, X-ray diffraction for structural imaging, phase contrast for enhanced contrast imaging and scanning transmission X-ray microscopy for spectromicroscopy. Two- and three-dimensional (confocal and tomographic) imaging methods were considered as well as the correlation of X-ray microscopy with other imaging tools. They pointed out that X-rays have the advantage to penetrate through a thick biological sample providing imaging of metals in brain tissues at regional, cellular, and sub-cellular spatial resolution. Two publications described how LA-ICP-MS was employed to investigate clinical disorders. Pozebon *et al.*[10] concentrated on the technical improvements during the last three years, referring to fast wash-out laser ablation cells, novel calibration strategies, nanoparticle uptake, applications and mapping of elemental distribution in biological samples. Meanwhile, Becker and Sussulini explained the formation of qualitative and quantitative maps showing distributions of elements in tissue sections of brain, cartilage, spinal cord, *etc.* in studies of neurodegenerative diseases.[11] Other MS approaches, reviewed by Lee *et al.*,[12] have been applied to metal-based anticancer drug research. Further discussion of developments in imaging is found in Section 6.2 of this Update. Cellular distribution of Zn has long been investigated in relation to its role in processes such as synaptic activity in neuronal cells. Earlier studies exploited fluorescent sensors to identify labile Zn pools. Carpenter *et al.*[13] reviewed work to show that mapping using MS and XRF techniques complement and strengthen data elaborated from sensors, with examples that included fertilisation of eggs and carcinogenesis.

As seen throughout this review and in Section 5, much innovation in the last few years has involved *nanomaterials*. Karadjova *et al.*[14] considered how materials such as magnetic nanoparticles, carbon nanostructures, metal oxides, noble metal nanoparticles, and ion imprinted polymers have been used for speciation applications such as analysis of food and biological samples. Single particle ICP-MS (spICP-MS) is a powerful technique to detect and characterise aqueous dispersions of metal and metalloid-containing nanomaterials. Recent advances in data acquisition, signal processing, and the use of alternative mass analysers (*e.g.* TOF-MS) provide a larger toolbox offering progress toward overcoming many of the challenges in the quantitative determination of nanoparticles. A review by Montano *et al.*[15] gave an overview of spICP-MS, discussing key issues for quantitative analysis of increasingly complex environmental and biological samples.

The feasibility of utilising LIBS for *food analysis*, was published by Markiewicz-Keszycka *et al.*[16] who suggested that the technique provided an alternative approach to time-consuming analytical methods. The review contained an overview of LIBS fundamentals, instrumentation and statistical data analysis and described recent progress and applications to assess the quality and composition of food products. It concluded that while the technology shows many advantages, sample preparation, matrix effects, spectral pre-processing and calibration still present challenges that require resolution.

Other *reviews relating to food analysis* are of interest. Taylor *et al.*[17] considered combining the distribution of organic As species in seafood with analytical aspects and consumption and toxicity data to identify gaps in current understanding. They highlighted that for organic As species further work is required: more complete As speciation across seafood types, particularly for arsenolipids; more RMs; more advanced toxicity testing is necessary to assess their effects; studies on metabolic pathways and individual variability, and distribution of As compounds in the body, to examine their toxicokinetics; and identification of biomarkers for As in seafood. To inform regulatory practices, a crucial missing link to understanding exposure is a full assessment of As in food that considers organic As compounds in seafood. Moreda-Piñeiro *et al.*[18] discussed the determination of Se and Se-compounds bioavailability, using both *in vivo* and *in vitro* tests. It was shown that results depended on the experimental conditions selected and the authors proposed that an internationally agreed standardised protocol for such experiments was necessary. Food traceability is of considerable commercial importance and we report on relevant work in these Updates (Section 8.3). Baffi and Trincherini[19] discussed recent results using the ^{87}Sr : ^{86}Sr isotopic ratio technique applied to vegetables, beverages, dairy products, meat and fish products. Summaries of work considered for this ASU are shown in Tables 1 and 2.

Table 1 Clinical and biological materials

Element	Matrix	Technique	Sample treatment/comments	Reference
Ag	Pulmonary epithelial cells	SF-ICP-MS	Study of the effect of NP diameter and tissue culture medium composition on AgNP uptake rates in cultured 16HBE14o cells	55
Ag	T84 human colonic epithelial cells	ICP-MS	Total Ag was measured in conjunction with other analyses following exposure of basal cells to AgNPs of different sizes and at different doses	103
Ag	Serum, environmental waters	SEC-ICP-MS	A rapid 8 min method for measurement of elemental mass size distribution of Ag and AuNPs. High ionic strength mobile phase (2% FL-70™ (strong alkaline detergent)/2 mM $Na_2S_2O_3$) ensured size independent elution of NPs from the column. The NP size distribution obtained agreed closely with that from TEM and this method had a higher mass sensitivity (1 pg) and comparable size discrimination (0.27 nm)	114
Al	Simulated body fluid, artificial saliva	ICP-MS	Evaluation of metal ion (Al, Ti, V) release from plasma electrolytic oxidation coatings used for dental and orthopaedic implants while immersed in normal and inflammatory simulated body fluids	142
Al	Human brain tissue	GF-AAS	Following microwave-assisted digestion, brain tissue from 12 patients with familial Alzheimer's disease was found to have Al content ranging from 0.01 to 35.65 μg g^{-1} dw with 58% of tissues having pathologically significant concentrations ≥3.00 μg g^{-1}	149
As	Erythrocytes, whole blood, plasma, urine and liver tissue	ICP-MS, HPLC-ICP-MS	In a case study of poisoning with iAs and Cr^{VI}, three days post exposure, blood As was 206 μg L^{-1}, erythrocyte Cr^{VI} was 4540 μg L^{-1}, blood and plasma total Cr were 2180 and 1070 μg L^{-1}, and liver As and Cr content was 0.9 and 11.7 mg kg^{-1} respectively. Speciation analysis of As showed the predominant species to be iAs, MMA and DMA	151
As	Urine	HPLC-HG-ICP-MS	Urinary concentrations of iAs, MMA and DMA in 9 year old Bangladeshi children ($n = 488$) showed a higher percentage DMA and lower iAs with respect to their mothers. The association of these concentrations with erythrocyte Se and folate was also investigated	121
As	Urine	HPLC-ICP-MS	In a Spanish population ($n = 124$), MMA and As^{III} were detected in 5.6% and 1.6% of subjects respectively while As^{V} was not found. Total As concentrations were higher than reported by other European studies but were composed of primarily AB and DMA	183
As	Urine	LC-ICP-MS	Concentrations of five As species were higher in infertile men with normal semen ($n = 101$) than fertile controls ($n = 61$), with As^{V} being 20-fold higher. The primary As methylation index (MMA/iAs) and As^{V} were most significantly associated with unexplained male infertility	184
As	Urine	HPLC-ICP-MS	Sum concentrations of iAs and MMA were assessed as a biological indicator of total iAs exposure in 330 exposed and 172 non-exposed subjects	150
As	Urine (NIST SRM 2669)	LC-ICP-MS	Fast speciation of As in 5 min using a short-length mixed bed ion exchange column with $(NH_4)_2CO_3$ mobile phase coupled to ICP-MS. The As^{III} was quantitatively converted to As^{V} with H_2O_2. The method achieved RSDs of 2.0 to 4.8% for all species and LODs from 0.003 to 0.051 ng g^{-1}. In urine samples, the sum of species measured corresponded to 62 to 125% of total As	185
As	Soft tissue and bone phantoms	SR-XRF, portable XRF	A comparison of results obtained using SR-XRF (monochromatic beam energy 15.8 keV) and portable XRF (Rh anode X-ray tube operated at 40 kV) for As in soft tissue phantoms and Pb in bone phantoms. Lower LODs were achieved for SR-XRF	93
Au	Serum, environmental waters	SEC-ICP-MS	See Ag, ref. 114	114
Au	Mouse organs	ICP-MS	Following intravenous injection of Tween® 20-conjugated AuNPs for 21 days in mice, quantification of total Au found highest concentrations in the bladder and hematopoietic bone tissue	108

Table 1 (*Contd.*)

Element	Matrix	Technique	Sample treatment/comments	Reference
Au	Fibroblasts, mouse organs	ICP-MS	*In vitro* uptake by fibroblasts of functionalised AuNPs and Au nanoclusters was evaluated by ICP-MS in conjunction with fluorescence confocal microscopy. *In vivo* studies of 9 mice treated for 24 h with 1.70 μg g^{-1} AuNPs showed different distributions of accumulation depending on the functionality of the NP	104
Au	Human placental co-culture microtissues	ICP-MS, LA-ICP-MS, TEM	Higher uptake and deeper penetration of AuNPs was demonstrated for smaller particles and those modified with Na carboxylate rather than PEGylate in an *in vitro* study	102
Au	Human skin hair follicles	ICP-OES, LA-ICP-MS	Evaluation of the distribution of hydrophobic, neutral and charged Au nanorods in hair follicles and skin	105
Au	Macrophage-like RAW 264.7 cells	Cluster SIMS	Chemical imaging of AuNPs using C_{60}^{+} primary ions in a single cell system. Fluorophore-functionalised AuNPs allowed visual confirmation of the intra-cellular location of NPs	133
B	Serum, whole blood, urine and drinking water	ICP-MS	Serum B concentrations in 194 pregnant women in northern Argentina were 0.73 to 605 μg L^{-1} (median 133 μg L^{-1}) correlating strongly with blood and urine concentrations and to a lesser extent with drinking water B (377 to 10 929 μg L^{-1}). Serum B >80 μg L^{-1} was inversely associated with birth length	153
B	Urine, rye grass (ERM-CD281)	ICP-OES	A fast and simple method for urine B biomonitoring using ICP-OES, which achieved precision ≤2% and recoveries of 102 to 109%. When compared with results obtained by Q-ICP-MS and SF-ICP-MS at low and medium resolution, there was good agreement for ^{11}B but suspected Ne^{2+} (an Ar impurity) interference on ^{10}B with all methods except medium resolution SF-ICP-MS	152
Ca	Serum	ICP-MS	A candidate reference method for serum Ca involved first spiking samples gravimetrically with Al internal standard then digestion with concentrated HNO_3 before dilution to measure concentration. The $^{44}Ca/^{27}Al$ ratios were measured in H_2 mode. Analytical figures of merit were CVs of 0.27 and 0.16% and recovery, 100.24%. Analysis of CRMs and comparison with a reference method were satisfactory	27
Ca	Anterior pituitary secretory granules	XRF microscopy, ICP-MS	A study of rat pituitary sections by XRF microscopy and subcellular sections by ICP-MS to localise and quantify Ca, Cu and Zn. The Ca concentration was approximately 10-fold higher than Zn and 50 times higher than Cu	135
Cd	Blood	GF-AAS	Reference ranges for blood Cd and Pb were determined for residents of Athens. The 95th percentile was 1.8 μg L^{-1} for blood Cd with a median of 1.2 μg L^{-1} in smokers *versus* 0.46 μg L^{-1} in non-smokers	147
Ce	Rat blood, urine faeces and organs	ICP-MS	Investigation of the bio-distribution and pharmacokinetic modelling of inhaled fresh and environmentally aged CeO_2 NPs. Most Ce was recovered in the lungs and faeces with no differences between fresh and aged NPs	100
Co	Biological tissues; lobster hepatopancreas (NRC TORT-2 and TORT-3)	VG-ICP-OES	Photochemical VG of volatile Co species dissolved in 50% CH_2O_2 through exposure to UV radiation (254 and 185 nm) for 10 s before detection by ICP-OES at 238.892 nm afforded a 27-fold increase in sensitivity compared with pneumatic nebulisation. Optimum generation efficiency was 42 ± 2%, the LOD was 0.4 μg L^{-1} and precision was 3% at 100 μg L^{-1}	73
Co	Hip fluid simulant	ICP-MS	A modified sample preparation procedure, utilising nano-porous ultra-filters to separate particles from free ions and complexes in solution was employed to investigate the release of ions (Co, Cr and Mo) from Co, Cr, Mo alloys during wear simulation in different media	137
Co	Whole blood	ICP-MS	A method for routine analysis of blood Co and Cr achieved an LOD for Co of 0.06 μg L^{-1}. Spiked whole blood and historical PT material were used to demonstrate method accuracy, precision and recovery. Short term room temperature stability (64 h) of blood samples was shown to be acceptable	138

Table 1 (*Contd.*)

Element	Matrix	Technique	Sample treatment/comments	Reference
Co	Urine, blood and plasma	ICP-MS	Wide fluctuations in urinary Co concentrations were observed through the working week in 34 occupationally exposed individuals. Mean urine Co concentrations were significantly correlated with levels of Co-haemoglobin adducts and whole blood Co. Half-lives of Co were determined to be 12.3, 9.1 and 5.3 days in blood, plasma and urine respectively	155
Co	Human heart tissue	ICP-MS	Heart tissue for Co, Cr and V measurement was prepared by closed-vessel microwave digestion. Accuracy was verified using RMs and the within run CV was <20%. Reference ranges were established from 80 non-metal hip implant heart tissues. The reference range for Co (mean ± SD) was 0.1039 ± 0.1305 μg g^{-1}	143
Cr	Hip fluid simulant	ICP-MS	See Co, ref. 137	137
Cr	Whole blood	ICP-MS	See Co, ref. 138. The LOD for Cr was 0.41 μg L^{-1}	138
Cr	Human heart tissue	ICP-MS	See Co, ref. 143. The reference range (mean ± SD) for heart Cr was 0.1523 ± 0.2157 μg g^{-1}	143
Cr	Erythrocytes, whole blood, plasma, urine and liver tissue	ICP-MS, HPLC-ICP-MS	See As, ref. 151	151
Cr	Exhaled breath condensate (EBC), urine	ICP-MS, LC-ICP-MS	Measurement of Cr^{III} and Cr^{VI} in EBC with separation of the Cr species *via* a micro-sized column in a cohort of 58 occupationally exposed workers demonstrated significantly higher concentrations compared with 22 controls	154
Cu	Anterior pituitary secretory granules	XRF microscopy, ICP-MS	See Ca, ref. 135	135
Cu	Erythrocytes	HPLC-ID-ICP-MS	Development of a candidate reference method for quantification of Cu, Zn-SOD in erythrocytes using species specific double and triple ID-MS. Sample preparation involved precipitation of Hb by addition of 3 : 1 EtOH : $CHCl_3$ followed by concentration of the supernatant using micro-centrifugation filters. The protein was then separated and quantified by strong anion exchange HPLC-ICP-MS. An expanded measurement uncertainty of ≤1.50% was obtained	65
Cu	Serum	MC-ICP-MS	Application of high precision Cu isotopic analysis to monitoring patients post liver transplant. Lighter isotope ratios were associated with persistence of poor liver function as well as seeming to predict disease recurrence	157
Cu	Serum	MC-ICP-MS	No significant differences were found between Cu isotope ratios measured following a new Cu isolation procedure, involving a Chelex-100 chelating exchange resin followed by an AG® MP-1 anion exchange resin, and the conventional procedure, which consisted of two passes through the AG® MP-1 resin. The method was applied to study diurnal variation of Cu isotopic composition ($n = 5$)	38
Cu	Human bone and tooth enamel	LC-MC-ICP-MS	A report of Cu and Zn isotope ratios in historical French bone and teeth remains found no sex-related differences in Cu isotope ratios but observed a decrease in Zn isotope ratios related to increased meat and fish consumption during the 20^{th} century	186
Fe	Serum	MC-ICP-MS	High precision Fe isotopic analysis of serum showed heavier Fe isotope ratios in patients with chronic kidney disease and Fe disorders compared with controls but not in erythropoietin-related anaemia	158
Gd	Bone phantoms	XRF	An *in vivo* XRF system, based on a ^{109}Cd source (5 GBq) was investigated for detection of Gd in doped bone phantoms. The LOD was 0.8 ppm. For phantoms coated with lucite as a tissue equivalent, LODs were 1.81 to 3.47 ppm	160
Gd	Brain and bone tissue	ICP-MS	In 9 patients with normal renal function given a single dose of non-group 1 Gd-based contrast agents, higher concentrations of Gd were measured in bone tissue and these correlated with Gd in brain	161
Gd	Rat brain and blood	ICP-MS	Concentrations of Gd were measured in 12 rats after high and low dosing regimens with gadodiamide contrast agents. Dose-	162

Table 1 (*Contd.*)

Element	Matrix	Technique	Sample treatment/comments	Reference
			dependent low levels of Gd were detected in brain one week after dosing (mean 2.49 nmol g^{-1}), which diminished to approximately 50% by 20 weeks	
Gd	Rat blood, CSF and brain tissue	ICP-MS	Measurement of Gd in rat blood, CSF and brain tissue, 24 h post administration of different high dose Gd-based contrast agents (1.8 mmol kg^{-1}), yielded no agent dependent differences. The pattern of Gd concentrations in CSF and brain tissue suggested CSF as an entry point into the brain	163
Hg	Hair	LA-ICP-MS, GC-ICP-MS	In 5 individuals exposed to Hg vapour 3 months previously, single point LA of hair samples (50 μm diameter at 1 mm intervals), using a ^{34}S internal standard followed by speciation analysis showed up to a 1000-fold increase in iHg concentrations at corresponding distances from the root. This was explained by direct adsorption of Hg vapour onto hair at the time of exposure	187
Hg	Human whole blood, hair and urine; caprine blood (NIST SRM 955c level 3); human hair (IAEA 085/086)	GC-ICP-MS	A method for simultaneous determination of MeHg, EtHg and iHg in various biological matrices with identical sample preparation and GC-ICP-MS measurement conditions was validated using the CRMs listed opposite. Species interconversion, particularly of EtHg into Hg^{II}, was observed and found to be dependent on the amount of Na tetrapropylborate added for derivatisation	122
Hg	Blood	ICP-MS	A UK study in 4044 pregnant women showed no significant association of maternal blood Hg concentration and anthropometric variables or gestational age at delivery. A negative association with birthweight was observed in non-fish eaters	188
Hg	Umbilical cord blood	ICP-MS	Mean total Hg, MeHg and iHg concentrations were 1.40, 0.95 and 0.13 μg L^{-1} respectively in umbilical cord blood from 263 pregnant women. Increased concentrations of MeHg were associated with higher pulse blood pressure while a similar increase of iHg was associated with lower systolic and pulse blood pressure	165
Hg	Urine (NIST SRM 3668, levels 1 and 2)	FI-CV-AAS	Online use of a Fe^{3+} catalyst in an FI system increased the vaporisation efficiency of organic Hg and eliminated sample pre-treatment. Optimisation enabled Hg^{2+} to be used as the calibration standard for both organic and iHg. An LOD of 0.14 μg L^{-1} was reported. Recoveries from CRMs and Hg^{2+}/MeHg-spiked urine ($n = 101$) were between 93.4 and 107.7%	86
Hg	Urine	AFS	The Hg in urine was extracted by SPE *via* active nano-Au coated Si material prior to thermal desorption and detection by AFS. From spiked urine, recoveries were 96.13 ± 5.34%. Results from occupationally exposed individuals were in good agreement with those obtained by conventional CV-AAS and CV-AFS. The LOD was 0.004 μg L^{-1} and RSDs were ≤4.2% ($n = 6$)	36
Hg	Bone (human proximal femur)	CF-AFS	In 96 patients undergoing total hip replacement, mean Hg content of the femoral neck and head were 37.1 ± 35.0 and 24.2 ± 35.0 ng g^{-1} respectively. An association was described with body mass index, differences in body anatomy and gender	189
Hg	Human teeth	fs-LIBS	Diffusion of Hg and other elements in the tissue surrounding amalgam tooth restorations was found to be more extensive in permanent teeth ($n = 8$) than in deciduous teeth ($n = 7$). Mapping of element distribution was achieved with a spatial resolution <100 μm	84
In	Urine, blood, air	ICP-MS	Samples from 494 Chinese smelting plant workers were analysed for In. Results were indicative of In exposure and there was a positive correlation between personal air and both blood and urine In concentrations	190
Mo	Hip fluid simulant	ICP-MS	See Co, ref. 137	137
Os	Human ovarian cancer cells	SR-XRF	Mapping of an Os-containing chemotherapy drug candidate in ovarian cancer cells using an SR-XRF nanoprobe	97

Table 1 (*Contd.*)

Element	Matrix	Technique	Sample treatment/comments	Reference
Os	Mouse organs, cell culture	ICP-MS	An Os-containing anticancer drug was quantified in organs of drug-treated mice by ICP-MS. Sample preparation involved addition of a stabilising solution (ascorbic acid, thiourea and EDTA) and avoidance of oxidising conditions. The LOD was 0.02 μg kg^{-1}. In spiked liver tissue, the RSD was 4% and recovery was 92%. When applied to cellular accumulation studies *in vitro*, cells were lysed with a non-oxidising buffer before addition of the stabilising solution	191
Pb	Blood	GF-AAS	See Cd, ref. 147. The 95th percentile for blood Pb in residents of Athens was 77 μg L^{-1}	147
Pb	Soft tissue and bone phantoms	SR-XRF, portable XRF	See As, ref. 93	93
Pb	Bone	XRF	A study demonstrating the feasibility of high-energy X-ray tube based XRF with a Cd Zn telluride detector for metal exposure assessment, achieving an LOD for Pb of 6.91 μg g^{-1} bone	94
Pb	Human teeth	SR-μXRF	Determination of the micro-distribution of Pb within teeth demonstrated that in incisors, Pb was primarily deposited in the secondary dentine region close to the pulp, co-localised with Zn, while in molars, Pb accumulated in the pulp and was co-localised with Ca	164
Pt	Plasma ultrafiltrate	ICP-MS	A method for measuring the chemotherapy drug, carboplatin, in plasma ultrafiltrate, prepared using Amicon Ultra 30 000 Da cut-off filters, followed by dilution in NH_3 EDTA. Bias was <6% and 12% at the LOQ. Precision CV's were <3%. The assay was applied to 10 clinical samples	166
Pt	Human lung carcinoma cells	HPLC-SF-ICP-MS	Quantification of carboplatin–DNA adducts was achieved using a species-specific double ID strategy with micro-flow HPLC RP separation coupled to SF-ICP-MS. The LOD was 0.2 ng Pt mg^{-1} DNA. Following validation using reference carboplatin–DNA spiked cell samples, the methodology was applied to cultured lung carcinoma cells exposed to carboplatin	167
Pu	Urine	LC-ICP-MS	Following addition of a ^{239}Pu internal standard to acidified urine and microwave digestion, ^{242}Pu was separated by extraction chromatography and detected by ICP-MS. A 30-fold improvement in sensitivity was achieved compared with a direct "dilute and shoot" method	39
Ru	Artificial cytosolic environment	CE-ICP-MS	Study of intravenous anticancer drugs, indazolium Ru–transport protein adducts, in an intracellular model containing glutathione (1–10 mM), ascorbic acid (10 mM), and citric acid (50 mM), demonstrated no transformation of the Ru compounds	192
Ru	Mouse blood cells, plasma and solid organs	ICP-MS, CE-ICP-MS, SEC-IC-ICP-MS	Distribution of a soluble Ru complex following intravenous administration in mice at different time points was assessed using separation techniques, CE and SEC-IC, followed by ICP-MS	116
S	Snake venom	ICP-QQQ-MS, ESI-QTOF-MS	Use of a hybrid elemental and molecular MS configuration to identify and quantify intact S-containing snake venom proteins *via* $^{32}S/^{34}S$ ID analysis	64
Se	Blood	CSDF-ME-GF-AAS	Continuous sample drop flow microextraction (CSDF-ME) coupled to GF-AAS was reported for speciation of Se in blood. The method involved extraction of Se^{IV}-ammonium 1-pyrrolidine dithiocarbamate complex by passing aqueous sample (5 mL) through carbon tetrachloride (32 μL) before injection into the graphite tube. Following optimisation, the LOD was 0.02 μg L^{-1}, between batch RSD ($n = 7$) was 4.2% and good enrichment and enhancement factors of 106 and 91 respectively were achieved. Total iSe was estimated after reduction of Se^{VI} with gentle boiling in 5 M HCl and subtraction of Se^{IV} from total Se concentration	123
Ti	Simulated body fluid, artificial saliva	ICP-MS	See Al, ref. 142	142

Table 1 (*Contd.*)

Element	Matrix	Technique	Sample treatment/comments	Reference
Ti	Blood, serum and hip fluid	ICP-OES	Validation of a method in clinical samples for Ti by ICP-OES using emission lines 336.1 and 371.0 nm and Y internal standard. The LOD and LOQ were 0.6 and 1.9 μg L^{-1} respectively. Bias was 3.3% and −1.0% for whole blood and serum respectively while intermediate precision was 10.9% and 8.6%. Higher Ti concentrations were measured in hip fluid samples (mean 5.1 μg L^{-1}) compared with whole blood and serum (median 2.4 μg L^{-1})	75
Ti	Serum	SF-ICP-MS	A prospective longitudinal study of serum Ti concentrations in 30 patients implanted with Ti ceramic composite cervical disc replacements. The LOD for Ti was 0.2 ng mL^{-1}	141
Ti	Human jawbones	ICP-OES, LA-ICP-MS, SEM-EDX	The Ti content of jawbones with dental implants ($n = 7$) assessed by ICP-OES was found to be significantly higher (mean 1940 *versus* 634 μg kg^{-1}) than controls. Particles (0.5 to 40 μm) were identified in bone marrow by SEM-EDX	128
Ti	Rat shinbones	SR-XRF	Diffusion of Ti in Ti-implanted shinbones of 6 adult rats was demonstrated by SR-XRF	139
Ti	Rat organs	ICP-MS	Report of bio-distribution of Ti in healthy young adult and elderly rats exposed *via* inhalation to 10 mg m^{-3} of a TiO_2 NP aerosol daily over 4 weeks. Immediately after exposure, high concentrations of Ti were found in the lungs but this was followed by translocation to extra-pulmonary organs (spleen and liver), particularly in elderly rats	98
Ti	Rat blood, tissues and excreta	ICP-MS	Measurement of Ti concentrations in rats following inhalation exposure to 15 mg m^{-3} of TiO_2 NPs over 6 h demonstrated initial accumulation in the lungs before translocation to the systemic circulation. Higher Ti concentrations were found in faeces *versus* urine	99
V	Urine	ICP-MS	Median concentrations of V measured in 816 Chinese maternal urine samples were higher in those with low birthweight babies compared with controls (3.04 *vs.* 1.93 μg g^{-1} creatinine). The odds of low birthweight were found to be increased 2.23 fold in mothers with urinary V ≥2.91 μg g^{-1} creatinine	193
V	Simulated body fluid, artificial saliva	ICP-MS	See Al, ref. 142	142
V	Human heart tissue	ICP-MS	See Co, ref. 143. The reference range (mean ± SD) for heart V was 0.0094 ± 0.0211 μg g^{-1}	143
Y	Cancer cells	ICP-MS	Development of a multifunctional probe to allow specific binding to cancer cells with subsequent dual imaging (down-conversion fluorescence and up-conversion luminescence) and quantification by ICP-MS *via* ^{89}Y detection. An LOD of 100 HepG2 cells and an RSD of 7.1% at 1000 HepG2 cells ($n = 7$) was reported	57
Zn	Serum and plasma	GF-AAS	Chloride interference and intolerance to high pyrolysis temperatures in a GF-AAS method for Zn was overcome by employing two matrix modifiers (Mg/Pa mixture combined with 1% (w/v) aqueous EDTA) and a high pyrolysis temperature of 1000 °C. Accuracy of the method was verified by direct comparison with ICP-MS and FAAS for analysis of an RM and analytical recovery studies	69
Zn	Anterior pituitary secretory granules	XRF microscopy, ICP-MS	See Ca, ref. 135	135
Zn	Human bone and enamel	LC-MC-ICP-MS	See Cu, ref. 186	186
Zn	CRMs; fish muscle, bovine muscle, pig kidney and human hair, serum and urine	MC-ICP-MS	Analysis of six biological CRMs to determine their stable Zn isotope ratios using the double-spike technique and high precision MC-ICP-MS (RSDs 0.04 to 0.13%)	25
Various (19)	Urine	ICP-MS	A study of the seasonal variation in urine metal concentrations involving 7 participants. Twelve elements were found to have significantly higher concentrations in the summer months	148

Table 1 (*Contd.*)

Element	Matrix	Technique	Sample treatment/comments	Reference
Various (9)	Urine	ICP-MS, LC-AFS	A study to determine reference values for first morning spot urines for Al, As, Ba, Ce, Mn, Sc, Ti, V and Y in 210 Chinese children, aged 2 to 12 years. The creatinine adjusted metal concentrations were significantly correlated with those in 24 h collections	31
Various (14)	Blood and urine	ICP-MS	A survey of metal concentrations in a cross section of 2000 individuals from a former heavily industrialised area of Northern France. Concentrations of most metals in urine were higher than those reported in the French National Survey for the same period although blood Pb levels were lower	30
Various (14)	Serum	SF-ICP-MS	A reference range study of 1400 pregnant women selected at random from the China Nutrition and Health Survey 2010 to 2012	29
Various (13)	Serum	TXRF	A study to determine serum concentrations of elements in 105 healthy volunteers from the Swietokrzyskie region in Poland by TXRF	194
Various (10)	Blood, serum and plasma	PIXE-PIGE	Techniques PIXE and PIGE were applied in external (in-air) microbeam configuration to determine concentrations of elements Br, Ca, Cl, Cu, Fe, K, Na, P, S and Zn in whole blood, serum and plasma. Very small volumes (10 μL) could be analysed directly with no sample preparation	96
Various (6)	Serum	ID-ICP-MS, ICP-OES, AAS, IC, ISE	Human serum CRMs for Ca, Cl, K, Li, Mg and Na at three concentration levels were developed and certified by a number of analytical methods. The expanded uncertainties ranged from 2.2 to 3.9%	26
Various (4)	Serum	ICP-MS	A sandwich-type immunoassay for serum neuron specific enolase, alpha-fetoprotein and C-reactive protein consisted of a Cs-doped magnetic multi-core NP for magnetic extraction and ratiometric ICP-MS measurement and three metal (Au, Cd, Y)/dye-doped SiNP probes for ICP-MS multiplex detection. The dye moieties also allowed confocal laser scanning microscopy imaging of the probes. No sample pre-treatment was required. The LODs varied from 0.35 to 77 ng mL^{-1} and recoveries from 83 to 125%	56
Various (10)	CSF	ICP-MS, ICP-AES	Concentrations of Ca, K, Mg, Na, P, Sr and Ti in CSF of patients with chronic neuropathic pain were found to be significantly higher than controls but the use of spinal cord stimulation had no effect	145
Various (4)	Saliva	TXRF	Measurement of salivary Cr, Cu, Fe and Ni demonstrated significantly higher Cr and Ni concentrations in patients with metal ($n = 30$) compared with aesthetic ($n = 30$) fixed orthodontic appliances but this did not reach significance *versus* controls ($n = 30$)	144
Various (4)	Liver	μXRF, SR-μXRF, XANES	Elemental distribution maps of Cu, Fe, Mn and Zn with resolution at the cellular level were obtained from a Wilson's disease liver biopsy specimen by SR-μXRF (beam size 4 μm). Oxidation states of Cu were identified by XANES	195
Various (4)	Bone and mucosal tissues	SR-XRF	A prospective pilot study investigating the incidence of elements (Ca, Fe, P, Ti) in bone and mucosal tissues around dental Ti implants with signs of peri-implantitis ($n = 12$). Analysis by SR-XRF revealed presence of Ti and an associated occurrence of Fe in 75% of samples	140
Various (4)	Breast cancer tissues	LA-ICP-MS	Application of LA-ICP-MS to assessment of Ca, Cu, Fe and Zn in breast cancer tissues found significantly higher concentrations in tumour areas compared with normal tissue and the distribution of elements was observed to be heterogeneous	127
Various (8)	Porcine nerve and fat tissues	LIBS	Study of elemental composition (C, Ca, H, K, Mg, N, Na and O) of fat and nerve tissue using LIBS with an Nd: YAG laser in open air and under normal stray light conditions	196

Table 1 (*Contd.*)

Element	Matrix	Technique	Sample treatment/comments	Reference
Various (9)	Xylem and embryo sac liquid of green pea (*Pisum sativum*)	HILIC-ICP-MS/ESI-FTMS, SEC-ICP-MS/ESI-FTMS	A general analytical methodology for large scale identification and quantification of metals, Ca, Co, Cu, Fe, Mg, Mn, Mo, Ni and Zn, and their complexes, in pea fluids involving two chromatographic techniques in conjunction with elemental and molecular MS detection	59
Various (5)	Plants; aquatic plant (BCR-670)	ICP-MS	Various digestion procedures for plant tissues were compared (dry-ashing, dry-ashing including a HF step and wet digestion using H_2O_2 and HNO_3) to enable measurement of rare earth elements Eu, Gd, Ho, La, Lu. Accuracy of the method was verified using the CRM opposite, RSDs varied from 1 to 4% and LODs were between 0.02 (Lu) and 13 ng L^{-1} (La)	34
Various (6)	Unicellular green algae (*Chlamydomonas reinhardtii*)	TEM, TEM-EDX, nanoSIMS	Chemical imaging by nanoSIMS of Ca, Cu, Fe, Mg, P, and Zn, employing a recently developed rf plasma oxygen primary ion source, achieved lateral resolution <50 nm. Parallel TEM of the same cell allowed relation of the ultrastructure to the spatial distribution of metals	136

2 Metrology, interlaboratory studies, reference materials and reference ranges

The metrological traceability of measurement results to the International System of units (SI) or, if not yet achievable, to other acknowledged units, is a key element to assure their comparability. For this reason, in the recently revised ISO/IEC 17025:2017 Standard, its importance was strongly remarked. However, metrological traceability is particularly difficult to achieve for chemical measurements in biological materials, owing to the complexity of analytical methods, the variability of the matrices and, in many cases, the difficulty to identify and/or maintain individual analytical species. *Certified reference materials (CRMs) play an essential role in establishing metrological traceability,* providing both the means for traceable calibration of analytical instruments and the tools to demonstrate that an analytical method is able to deliver accurate analytical results. Therefore, the scientific community relentlessly continues to put effort in their production and characterisation.

Chronic exposure to As, through the diet, is a potential health risk for the general population, however As toxicity depends on the chemical structure of the As species, with iAs being the most toxic. In food of marine origin, relatively high levels of As can be observed, but mostly as AB, a nearly non-toxic As species. The speciation of the five most common As species observed in food (As^{III}, As^{V}, AB, DMA, MMA) generally requires complex analytical procedures, for which calibration standards traceable to the SI are only available as iAs solutions. Owing to the non-equivalent response of As compounds during speciation procedures, specific standard solutions for individual As species are necessary for calibration, to assure the metrological traceability, and hence comparability, of the measurement results. To this aim, Lee and co-workers[20] at the Korean Metrology Institute, prepared and characterised a CRM for AB, starting from AB bromide (98% purity). The total As content in the solution was determined by INAA, recognised as a primary method for the measurement of elemental As. Trace impurities of other As compounds were quantified by HPLC-ICP-MS. To verify the complete separation of AB from other As species, the content of AB was further determined by the same chromatographic technique using a different column (Zorbax 300 SCX) and 4 mmol L^{-1} pyridine buffer at pH 2.3, as the mobile phase. The content of As as AB was determined by an As-specific mass balance method. This involved calculating the difference between the total mass fraction of As, determined by INAA, and the sum of the impurities, as mass fractions of As, determined by HPLC-ICP-MS. The uncertainty budget, including the contributions of all analytical steps, was calculated according to the "Guide to the expression of uncertainty in measurement" (JCGM 100). The content of AB, as As mass fraction, was certified as 51.28 mg kg^{-1} with an expanded uncertainty of $\pm$1.17 mg kg^{-1} ($k = 2$, approximately at 95% CL). This value was verified successfully by submitting the CRM to an international comparison among National Metrology Institutes (CCQM-K97 "Measurement of arsenobetaine standard solution and arsenobetaine content in marine fish."). The report is available at http://iopscience.iop.org/article/10.1088/0026-1394/54/1A/08003.

Besides being calibrators, *matrix specific CRMs are also important to assess the overall method performance during validation and to monitor the quality of results over time.* Shin and co-workers[21] developed an apple juice CRM, including As and As species (As^{III}, As^{V} and DMA), Cd and Pb as the reference analytes, starting from a commercially available apple juice, containing negligible amounts of the target elements. The item preparation and assessment were carried out according to the requirements of ISO Guides 34 and 35. After filtration and addition of 1.2 g L^{-1} Na benzoate as a preservative, the material was spiked with known amounts of the analytes. After homogenisation, 100 mL aliquots were placed in 125 mL HDPE bottles, flushed with N_2 for 15 s, sealed and stored frozen at -20 °C. Homogeneity and stability studies (as well as the assignment of

the reference values) were carried out in a single laboratory by SF–ICP-MS (As), HPLC-ICP-MS (As species) and ID-ICP-MS (Cd, Pb). The method for the determination of As species was validated in-house using rice flour CRMs, owing to the lack of similar matrix CRMs. Combined relative standard uncertainties (u_c%) were evaluated as 2.45% (Cd), 2.84% (Pb), 3.95% (As), 4.74% (iAs) and 4.30% (DMA), respectively. The uncertainty budgets indicated long term stability (4.5 months) as the major uncertainty contributor for As (3.88%), Cd (2.40%) and Pb (2.76%). For iAs and DMA, the uncertainty associated with the characterisation (4.07% and 3.66%) had the largest impact. The certified mass fractions (±expanded uncertainty, $k = 2$, 95% CL) were: 0.185 ± 0.015 mg kg^{-1} (As), 0.124 ± 0.012 mg kg^{-1} (iAs), 0.220 ± 0.011 mg kg^{-1} (Cd), 0.0601 ± 0.0052 mg kg^{-1} (DMA) and 0.245 ± 0.014 mg kg^{-1} (Pb). Unfortunately, only 54 units were prepared, but the information gained may be useful for future batch production.

Since iAs was identified as the most toxic As species in food and drinking water, the need has emerged for establishing harmonised analytical methods for iAs in various food commodities to be applied in assessment and pre-regulatory stages. de la Calle *et al.*[22] reported the inter-laboratory validation, by means of a collaborative trial (IMEP-41), of an analytical method for the quantification of iAs in food by FI-HG-AAS. Sample pre-treatment consisted of releasing As species from the matrix by incubation with concentrated HCl, followed by extraction of iAs with $CHCl_3$ and back-extraction into an acidic medium. Analytical performances were assessed according to the statistical protocol described in ISO 5725. The test items were seven RMs, covering a broad range of food matrices (cabbage, fish protein, mushrooms, mussels, rice, seaweed (hijiki) and wheat) and concentrations ranging from 0.074 to 7.55 mg kg^{-1}. Assigned values for iAs mass fractions were either provided by the respective CRM producers (rice and seaweed), derived as consensus value from a proficiency test (mushrooms) or determined by expert laboratories with demonstrated measurement capabilities in this field of analysis. The repeatability RSD% ranged from 4.1% to 10.3%, while the reproducibility RSD% ranged from 6.1 to 22.8%. No significant bias could be identified for the matrices investigated.

Acceptable limits for the content of iAs in rice, recently established by CODEX and other international legislation, together with the large consumption of this food commodity, impose the need for *rapid methods to determine compliance of rice batches with the stated limit values before they are distributed to markets.* As XRF spectrometry is able to directly analyse solid samples the technique has been used to assess levels of Cd in rice grain samples. Although limited to the determination of total As content, XRF spectrometry also carries the potential for rapid screening for the As content in rice and several rice flour CRMs exist. However, in XRF spectrometry, responses are affected by differences between the sample matrices and/or physical form of the sample. With these caveats in mind and, following from their previous work on the preparation of rice grain calibration standards for the determination of Cd, Nakamura *et al.*[23] applied the same procedure to the calibration of As in cereal grains by XRF spectrometry. A preliminary assessment of suitable As species for spiking, led to the choice of DMA as the best option, providing approximately 100% recovery, whereas As^{III} was lost during the treatment. Aliquots of rice grains (10 g) were added to 100 mL MeOH containing DMA, to achieve final mass fractions of As between 0 and 5 mg kg^{-1}. The solvent was then removed by heating on a hot plate at 150 °C for 1 h. After cooling at room temperature, 5.0 g aliquots of each calibration standard were packed into polyethylene cups and covered with a 6 μm thick polypropylene film. Calibration curves produced with these materials showed good linearity (r = 0.999). The results obtained by XRF in commercially available samples of brown and white rice grains and As spiked barley grains compared well with those obtained by ETAAS after acid digestion.

Uribe and co-workers[24] reported the preparation and certification of *a CRM for the content (ng g^{-1}) of Al, As, Cd, Cr, Cu, Mn, Ni, Pb and Zn in drinking water*, produced by the Peru National Institute of Quality (INACAL), with expanded relative uncertainties between 0.8% and 1.9%. The target mass fractions were set according to national maximum permissible limits. The assigned values were derived from both the gravimetric preparation and the subsequent analytical measurements by means of ETAAS or FAAS, using the bracketing calibration technique, in a single laboratory. The measurement capabilities of INACAL for these analytes in drinking water were confirmed by successful participation in a comparison with primary methods organised by the Inter-American Metrology System (SIM-QM-S2). The assigned values were monitored for 24 months using ETAAS or ICP-AES. The CRM production was carried out according to the requirements of the ISO Guides 34 and 35 and uncertainties were evaluated according to established international guidance (JCGM 100 "Guide to the expression of uncertainty in measurement" and Eurachem guides).

Isotopic ratios are increasingly investigated in biomedical research, together with elemental concentrations, to highlight small variations in the metabolic patterns of essential and toxic elements, although the cost, time and skill required for such measurements may hamper their wider application. To aid such research, Moore and co-workers[25] undertook high precision measurements of the ^{66}Zn : ^{64}Zn ratio in several biological CRMs and RMs, of human and animal origin, such as human hair, serum and urine, fish muscle, bovine muscle and pig kidney, using MC-ICP-MS with an Aridus II sample introduction system and the double spike technique. A complex multi-step sample preparation procedure was necessary, consisting of microwave-assisted digestion with a 3:2 mixture of 15.4 mol L^{-1} HNO_3–H_2O_2. This was followed by evaporation of the digests to dryness and re-solubilisation with 2 mol L^{-1} HCl to achieve approximate concentrations of 1 μg mL^{-1} Zn. Aliquots of these diluted solutions, containing either ~250 or ~800 ng Zn, were mixed with known amounts of the tracer, highly enriched with ^{64}Zn and ^{67}Zn, to yield a molar ratio of tracer to natural Zn of 1 ± 0.05. The resulting solutions were dried, re-dissolved in 6 mol L^{-1} HCl, left at 130 °C overnight to equilibrate, then dried again and re-dissolved in 1 mol L^{-1} HCL prior to undergoing anion exchange chromatography to separate Zn from other matrix components. The eluate (0.01 mol L^{-1} HCl) was dried,

then treated twice with 50 μL of 15.4 mol L^{-1} HNO_3, followed by evaporation to dryness, to substitute Cl^- with NO_3^- ions. The solutions presented for instrumental analysis were prepared in 0.1 mol L^{-1} HNO_3. The relative differences (‰) between the ^{66}Zn : ^{64}Zn ratios, in the RM samples relative to the certified isotopic standard IRMM-3702 indicated limited variability for five of the tested RMs (−0.30 ± 0.10‰ for ERM-BB184 bovine liver; −0.34 ± 0.04‰ for ERM-BB422 fish muscle; −0.65 ± 0.13‰ for ERM-BB186 pig kidney; −0.31 ± 0.04‰ for ERM-DB001 human hair and −0.05 ± 0.04‰ for Seronorm Trace Elements Urine L^{-1}). For the blood serum RM (BCR-639) a larger difference was observed (−3.29 ± 0.12‰) confirming previous literature data.

The measurement of electrolytes in human serum is a routine task in clinical laboratories, necessary for the diagnosis and monitoring of pathological conditions and therapeutic treatments. A number of CRMs exist to support these measurements, however, only few seem to simultaneously fulfil the requirements for range of analytes, levels of concentrations and physical status similar to those in patient samples. A new set of three serum CRMs was prepared by adding high purity chloride salts to pooled human serum and certified for the mass fractions of Ca, Cl, K, Li, Mg and Na, by the group of Feng *et al.*[26] at the Chinese National Metrology Institute. The target concentration levels were within ±20% of the values observed in serum of healthy subjects. The certified values for Ca, K, Li and Mg were obtained by in-house primary methods, based on double ID-ICP-MS. To overcome polyatomic interferences affecting the accurate measurements of one or more isotopes of Ca, K and Mg, measurements were carried out using "cold" plasma conditions (RF power set at 750 W) and H_2 as the collision gas, at a flow rate of 6.0 mL min^{-1}. The assigned values for each of the two other elements were determined from the results of two independent reference methods (AAS and ICP-AES, for Na; combustion-hydrolysis IC and ICP-MS for Cl). An informative value was provided for the mass fraction of ionised Ca^{2+}, obtained by ISE. A 14 month stability study carried out under storage conditions (−20 °C) did not show significant differences in the measured values for any of the elements or levels. The uncertainties of the values assigned to the CRMs were estimated by combining the contributions of the measurement step, between-bottle homogeneity and long-term stability, to give expanded uncertainties for the certified values ranging from 2.2% to 3.9%. Another Chinese group, led by Zhang,[27] developed and validated, through analysis of CRMs and successful participation in international inter-laboratory comparisons, an ICP-MS method for the determination of Ca in serum. The procedure consists of gravimetric spiking of the samples with Al, as internal standard, followed by digestion with 69% HNO_3, dilution of the digest and measurement of the ^{44}Ca : ^{27}Al ratio using H_2 as the collision gas at a flow rate of 4 mL min^{-1}. The bracketing approach was applied for quantification. The RSD% was <0.27% and analysis of two NIST SRMs (4 concentrations levels) yielded bias values between −0.54% and 0.01%. The advantages of the proposed method were claimed as simplicity and low cost, in comparison with ID methods, which require highly enriched isotopes, expensive instrumentation, such as TIMS or SF-ICP-MS, and very skilled staff. In addition, the proposed method overcomes the potential bias problems associated with flame temperature, sample introduction and matrix effects in FAAS, achieved a better LOD than ICP-AES and the analytical step takes only 20 s in comparison with almost 10 min for analysis by IC.

Besides the accuracy of analytical measurements, an *appropriate and harmonised choice of the "sample" to be analysed can be a critical issue for the comparability of measurement results and related judgements*, *e.g.* compliance statements in regulated areas of testing. Most of the available PT items and CRMs represent homogenised matrices, either as lyophilised powders or pastes. The organisers of the proficiency test IMEP-118,[28] for the determination of the As, iAs, Cd, Hg, Pb and Sn mass fractions in canned vegetables, addressed this issue by choosing to prepare a test item (peas in brine in a glass jar) identical to those available on the market and potentially subjected to official food controls. After preliminary studies of elemental uptake, acid cleaned glass jars were manually filled with ~99 g of frozen green peas and 75 mL of a brine solution, spiked with the elements of interest (0.01 mol L^{-1} HCl, 0.3 mg L^{-1} As^V, 0.3 mg L^{-1} Cd, 0.2 mg L^{-1} Pb, 470 mg L^{-1} Sn and 6.9 g L^{-1} NaCl). Assigned values, for both the drained and whole material, were determined by five expert laboratories, selected on the basis of their experience and having accreditation for elemental analysis in food matrices. Both the total As and the iAs mass fractions were determined, using methods based on mild extraction procedures and HPLC-ICP-MS. Depending on the analyte and the choice of "sample" to be analysed between 74% and 98% of the participants achieved satisfactory analytical performances. Criticalities were identified: the potential binding of As^V to proteins, thus reducing its availability under mild extraction conditions, the limited number of participants (41 out of 123) reporting results for iAs and the lack of a harmonised approach on the choice of the "sample" (drained peas or whole sample) to be analysed.

Reference ranges for essential nutrients and for potentially toxic agents in biological fluids and tissues have been recommended for many years. However, several factors, such as ethnicity, residence, lifestyle habits, physiological conditions, age and sex, are known to influence such values and, therefore, additional, well designed studies, taking account of these variables are important. In this review year, three papers reported reference ranges addressing specific population groups or areas. The China Nutrition and Health Survey is a national cross-sectional study involving all areas of the country. As part of the 2010–2012 survey, Xiaoguang Yang *et al.*[29] determined the concentrations of 14 trace elements (As, Cd, Co, Cr, Cu, Fe, Mn, Mo, Pb, Rb, Se, Sr, V and Zn) in serum samples collected from 1400, randomly chosen, pregnant women, aged between 18 and 44 years (mean ± SD: 27.0 ± 4.5 years). Measurements were carried out by SF-ICP-MS, after 1 + 19 dilution with 0.5% (v/v) HNO_3. Data were analysed according to age, residence in urban or rural regions, anthropometric status (by the 4 categories: underweight, normal weight, overweight and obese) and duration of pregnancy (<12 weeks; 12 to <28 weeks; >28 weeks), using the Kruskal–Wallis test and linear model factorial analysis. The authors concluded

that, for some elements, remarkable changes were observed, according to the factors considered, but did not address their relevance in comparison with established findings or potential exposure. For example, women resident in rural regions showed significantly ($p < 0.05$) lower serum concentrations of As, Cd, Se, Pb and V, in comparison with those living in urban areas, and higher levels of Mn, Mo and Sr. To our knowledge, the observed ranges (including variations associated with age or pregnancy) for Cu, Fe, Se and Zn were similar to those generally applied in hospitals in other countries. On the other hand, the concentrations (2.5^{th}–97.5^{th} percentiles) reported for Co (57.0–1130.0 ng L^{-1}), Cr (219.8–4287.7 ng L^{-1}) and Mn (1.2–8.4 μg L^{-1}) were significantly higher than the currently accepted reference ranges. Given the notably higher levels of these elements in erythrocytes, sample contamination or significant exposure must be considered. Since Cd and Pb are usually determined in whole blood for the same reason, the observed values for these two elements may also need further investigation.

Another cross-sectional study (Nisse *et al.*[30]) examined the levels *of 14 elements (Al, As, Be, Cd, Co, Cr, Hg, Mn, Ni, Pb, Sb, Tl, V and Zn) determined by ICP-MS in blood and urine samples* from 2000 adult subjects representing the population of Northern France (IMEPOGE, 2008–2010). Age, sex and smoking habit were the determinants included in the study, whereas no exclusion was made for subjects who may have been occupationally exposed. Potential contamination from the test tubes used for the collection of blood samples was highlighted for Sb, leading to the exclusion of most of the data from further analysis. The survey results were compared with those obtained in several similar studies in other countries as well as in the French National Survey on Nutrition and Health, all carried out over approximately the same period. For most elements, the mean blood and urine levels were generally higher than those observed in other countries except for South Korea and China, owing to persisting environmental contamination from previous industrial activities.

3 Sample collection and preparation

3.1 Collection, storage and preliminary preparation

In last year's review we referred to two articles in which concentrations in spot urine samples were compared to results adjusted to creatinine concentration and to 24 h excretion. Conflicting results were reported. Now Zhang *et al.*[31] provide *further results relating to the timing of urine sample collection (morning first-spot or 24 h sample) on the reference values of nine elements* (Al, As, Ba, Ce, Mn, Sc, Ti, V and Y) in urine. Samples were collected from 210 children (2 to 12 years) in three provinces (Guangdong, Gansu and Hubei) of China. First-spot morning and 24 h urine samples were collected in acid cleaned PE bottles, for one day (186 children) and three consecutive days (24 children). Samples were acidified with 1 mL 5% (v/v) HNO_3, then stored at −20 °C until required. After thawing and mixing for at least 5 min, 15 mL of urine was digested with 3 mL HNO_3 and 2 mL H_2O_2 in a microwave oven, then diluted to 30 mL with ultrapure water and stored at 4 °C until analysis by ICP-MS. For As determination, urine samples were diluted (1 + 4) with ultrapure water and stored at 4 °C until measurement by LC-AFS. It was found that the early morning samples, adjusted for creatinine correlated significantly ($P < 0.0001$), with 24 h excretion. However values for R^2 ranged from 0.820 (Al) to 0.460 (Ti). Reference intervals in ng mg^{-1} creatinine were stated as 1.63–2653 (Al), 0.20–53.42 (As), 3.71–116.8 (Ba), 0.02–2.27 (Ce), 1.36–25.29 (Mn), 0.002–0.483 (Sc), 0.67–91.77 (Ti), 0.24–8.59 (V) and 0.01–0.65 (Y).

Xiong *et al.*[32] investigated possible *trace element sample contamination from 13 different blood collection tube types* available in China. The vials were tested by addition of water and 10% HNO_3 and 20 elements determined by ICP-MS. With this protocol, all tube types would potentially cause the concentration of at least one element in the blood sample to be significantly increased above the reference interval. Most tubes would influence the results for several elements. It should be noted that the solutions used are not equivalent to human blood and that 10% HNO_3 is an aggressive medium likely to extract more than might happen with blood. Nevertheless, experienced analysts will be aware that collection tubes can contaminate samples. Certain elements are always liable to be affected by impurities are sometimes unpredictable with variations from batch to batch and even from tube to tube within a batch.

As part of a project to develop a procedure to measure Pt in plasma, urine and tissues, Zhang *et al.*[33] found that Pt concentrations in calibration solutions, stock solutions and processed *samples were stable* after three freeze–thaw cycles and for up to three months.

3.2 Digestion, extraction and pre-concentration

3.2.1 Clinical and biological materials. Except for food samples, our Updates do not refer often to *plant materials*. Masson and Dalix[34] reported a comparison of methods to digest plant samples in preparation for the determination of REE concentrations using ICP-MS and, as digestion is widely applied to clinical and other biological samples, this work is relevant to this review. It was shown that dissolved solids (0.1–1.0%) decreased the REE ICP-MS signals but that correct results were obtained with an In internal standard. Dry-ashing, dry-ashing with an HF step and wet digestion using H_2O_2 and HNO_3 were compared and the results demonstrated that simple dry-ashing was sufficient for plants. Accuracy of results was demonstrated by analysis of a BCR CRM. Detection limits were between 13 and 0.02 ng L^{-1}, for La and Lu, respectively.

Carbon materials for solid phase extraction have long proved popular. A procedure to prepare limited quantities of material was developed by Chen *et al.*[35] for determination of Hg. Milligram amounts of sample solution in a volume of 100 μL were extracted with multiwall-carbon tubes (MWCNT) and this single drop taken for solution electrode GD-CV-AFS. With a 1 mg sample the LOD was determined as 0.01 mg L^{-1}. Advantages of the method included minimal sample dilution, low blank, high sample introduction efficiency, high sensitivity and minimal toxic chemicals.

Two publications refer to the use of *gold nanoparticles for the extraction* of Hg from biological samples. In the method developed by Schlathauer *et al.*[36] Hg in urine was separated with a nanogold-coated silica material and determined by AFS. Recovery from Hg spiked real samples was 96.13 ± 6.34% and samples analysed using this procedure and by CV-AAS and CV-AFS gave results that were in very good agreement. The LOD for the method was reported as 0.004 μg L^{-1} and the RSD% was <4.2%. Treated samples showed no loss of Hg when stored at 30 °C for up to a week. Hsu *et al.*[37] developed a similarly innovative approach to extract Hg^{2+} from CSF, dialysates and water. Nanoparticles with a gold core and iron oxide shell, functionalised with L-cysteine were used to adsorb the analyte ions prior to determination by ICP-MS. Validation of the method was demonstrated by analysis of a CRM and by recovery studies with results of 101.5–109.3%. Compared with conventional SPE this procedure was rapid and did not involve a desorption step.

In our recent Updates we have referred to the research work of Vanhaecke and colleagues directed at determination of *Cu isotopes in serum*. To achieve accurate results in a matrix in which elements such as Ca and Na are at much higher concentrations than the Cu, Lauwens *et al.*[38] extracted the alkali and alkaline earth metals using Chelex-100 ion exchange resin, followed by further purification of the Cu-fraction with AG MP1 anion exchange resin. The Cu isotope ratios were then determined by MC-ICP-MS. This procedure afforded low blank values, associated with lower amounts of acid required, and improved precision compared to other methods. Analysis of samples collected at time intervals throughout the day showed no diurnal variation in the serum Cu isotopic ratios.

Occupational exposure to Pu is monitored by analysis of urine samples. Current methods for separations and analysis by alpha spectroscopy are lengthy and require long count times. To avoid this, Gallardo *et al.*[39] proposed using ICP-MS after microwave heating digestion and separation of the Pu using an Eichrom-TRU resin column. Urine samples were acidified and ^{239}Pu added as an internal standard. The *pre-concentration* step provided a 30-fold improvement in sensitivity compared to a simple dilution approach.

3.2.2 Foods and beverages. The *importance of matching the digestion/extraction process with the determination technique* was highlighted by Japtag *et al.*[40] who investigated several sample preparation techniques prior to measurement of SeMet and SeCys in seafood. Although good recovery rates were obtained with methanesulfonic acid, the low pH required was not compatible with most HPLC columns and also degraded the species being determined. Enzymatic hydrolysis with protease type XIV also gave good recoveries but the instability of SeCys required a prior derivatisation using iodoacetamide. Conventional heating (37 °C, 20 h) and microwave assisted heating (45 °C, 45 min) gave similar recoveries although the former produced better recovery for fish tissue. The authors concluded a two-part approach was needed: SeMet was measured after protease hydrolysis and SeCys required derivatisation with carbamidomethylation prior to hydrolysis. Both species were separated using SEC followed by C8 ion-pair RP-HPLC-ICP-MS and the recoveries were 97 ± 9% and 85 ± 9%, respectively. The performance of a new high-pressure microwave-assisted flow digestion system, developed to digest juice and milk samples, was evaluated by Marques *et al.*[41] The system comprised of a coiled large volume reactor (13.5 mL) inside an autoclave pressurised with N_2 gas (40 bar) heated with 500 W microwave power and with 5.0 mL min^{-1} carrier flow rate. Milk samples were digested with HNO_3 (10.5 mol L^{-1}) with prior emulsification by ultrasound; residual C concentrations were 23% and 25% for skimmed and whole milk. Juice concentrate (sugars 730 g L^{-1}) required a slightly modified mixture of 3.7 mol L^{-1} HNO_3 and 0.3 mol L^{-1} HCl. There were no statistical differences in precision between the flow method and standard batch mode for most elements analysed by ICP-AES, with exception for Fe in whole milk.

Various *modifications to liquid–liquid microextraction for heavy metals determination* in food continue to be developed for use with less-sensitive spectrometric techniques. Magnetic ionic liquids (IL) were used by Wang *et al.*[42] to facilitate the separation of a Se-containing complex formed with 2,3-diaminonaphthalene. A vertical shaker allowed mixing of the aqueous rice sample with the extractants and a magnet was employed to retain the IL (1-butyl-3-methylimidazolium tetrachloroferrate) at the bottom of the microtube for determination by ETAAS. An LOD of 0.016 μg L^{-1} was reported with a RSD of <3% for Se^{IV}. The methodology was used for speciation of Se^{IV} and Se^{VI} in different rice samples. A pressure-induced IL, namely {1-hexyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide} extraction approach was used to extract the hydrophobic complex As-DDTC at pH 4.[43] This increased the phase transfer ratio which significantly increased the recovery of the As–DDTC complex to give an enhancement factor of 87.5. Determination of As by HG-AAS gave an LOD of 0.016 μg L^{-1} and RSD of 4.89%. Another approach used the IL trihexyl(tetradecyl)phosphonium decanoate to extract a Se^{IV}–APDC complex with a 90% efficiency and 100-fold pre-concentration factor.[44] The LOD of the Se determination by ETAAS was 5 ng L^{-1} and the method was applied to the determination of Se in *allium* and *brassica* species. Javedani-Asleh *et al.*[45] described a ligand-free extraction process where Br^- was used to complex Tl^{III} in the presence of cetylpyridinium chloride which was then extracted into MeOH–$CHCl_3$. Analysis by ETAAS, achieved an LOD of 0.03 μg L^{-1} and an RSD of 4.1%. Good liquid mixing of a chelating agent and easier separation of the chelated analyte when cold solidified, was used to determine Cd in herb samples.[46] After digestion of dried herbs with HNO_3 and H_2O_2, 1-(2-pyridylazo)-2-naphthol (PAN) in the liquid phase was used to extract Cd. The solvent was undecan-1-ol whose melting point was quoted as 19 °C. Optimised extraction conditions were a PAN concentration of 5 mmol L^{-1}, and an extraction time of 20 min at 65 °C with stirring at 1000 rpm. Buffer was then added to achieve pH 9. The LOD and LOQ using ETAAS were 0.0052 and 0.017 μg L^{-1}, respectively; the RSD at 1 μg L^{-1} Cd was 2.67% with a pre-concentration factor of 22.

Multiwall carbon nanotubes (MWCNT) continue to be popular for SPE although they themselves may contain transition metal catalyst contaminants such as Co, Fe and Ni. However, He *et al.*[47] combined MWCNT with matrix solid-phase dispersion

(MSPD) techniques for the determination of As, Cd, Cr and Pb in single rice grain samples with ICP-MS. Equal masses (*ca.* 0.02 g) of rice and MWCNTs, previously washed with 1 : 1 HNO_3-: H_2SO_4, were ground to a paste then blended with 1% HNO_3-: HCl (3:1, v/v, 2 mL) and centrifuged. The supernatant was analysed directly by ICP-MS yielding LODs of 5.0, 0.6, 10 and 2.1 ng g^{-1}, for As, Cd, Cr and Pb respectively, with RSDs <7.7%. Four CRMs were analysed with no significant difference (at 95% CL) between the certified and measured concentrations. The method compared well (R^2 > 0.94) with standard microwave digestion determined across 30 samples while the new MWCNT-MSPD method allowed a 100-fold reduction in sample size. Other workers in China[48] also used the same MWCNT-MSPD preparation techniques to facilitate the determination of Hg in limited size fish organ samples. The Hg species contained in 1 mg tissue were extracted into 100 μL of solvent (0.5% L-cysteine–4% HCOOH), and total Hg quantified by AFS following conversion to Hg^0 using a single-drop discharge-induced CV-GD system. An LOD of 0.01 μg L^{-1} was achieved with RSDs of 5.2% and 4.6% at 2 and 20 μg L^{-1}, respectively. Another application of the MSPD technique combined with graphitised carbon black, was employed by Liu *et al.*[49] to clean up cold-precipitated extracts of vegetable oil–MeOH for the determination of organotin compounds. Filtered extracts were separated by C_{18} RP-HPLC coupled to ICP-MS allowing quantification of four Sn species (DBT, TBT, DPhT, TPhT) in various edible vegetable oils, with LODs ranging from 0.28 to 0.59 μg L^{-1} and LOQs of 0.93 to 1.8 μg L^{-1}.

4 Progress with analytical techniques

4.1 Mass spectrometry

Reports involving *single particle ICP-MS* (spICP-MS) this year encompassed a broad range of elemental NPs and saw application of the technique to food and biological tissue matrices. Difficulties surround extraction of NPs for analysis without affecting the original NP characteristics, as well as achieving small particle size LODs in the presence of background dissolved ions. Ramos *et al.*[50] assessed the effects of *in vitro* digestion on the fate of AgNPs from AgNP-spiked chicken meat and a 40 nm AgNP standard. Comparison of two digest extract homogenisation protocols prior to SP-ICP-MS showed that AgNPs remained more intact with sonication for 90 s *versus* vortex mixing for 60 s. Influence of matrix components in the spiked chicken meat was evident with only 13% of AgNPs reaching the intestinal wall compared with 81% from the standard. The method achieved a particle size LOD of 20 nm. A second report demonstrated the accumulation of NPs in proteinase K-digested liver and egg yolk, following oral administration of 20 nm PVP-coated AgNPs to hens.[51] A smaller size LOD of 10 nm was achieved with a 2 ms dwell time through the use of SF-ICP-MS rather than Q-ICP-MS. A study to determine the size distribution of CeO_2 NPs in plant shoots, with a macerozyme R10 sample digestion and dwell time of 0.1 ms, achieved a modest particle size LOD of 23 to 25 nm.[52] Lower LODs of 18 to 20 nm for CeO_2 NPs were demonstrated in the simpler matrix of drinking water in a report investigating the efficiency of water treatment processes.[53] For ZnO NPs, LODs were poorer (35 to 40 nm) because of dissolved Zn background although the use of shorter dwell times had allowed omission of an IEC separation step. The first published study on the contribution to Pb exposure by PbNPs in food was claimed by Kollander *et al.*,[54] in which PbNPs were measured in game meat shot with Pb bullets. Higher than ideal LODs (40 to 80 nm) were observed in the meat matrix and longer enzyme digestion protocols caused partial dissolution of the PbNPs. An investigation into uptake rates of AgNPs in pulmonary epithelial 16HBE140 cells converted total Ag concentration, measured by SF-ICP-MS, to NP numbers using a formula incorporating total particle diameter and coating thickness.[55] This approach did not provide any information on the intactness or aggregation of the NPs.

Two papers in this review period used *NP probes in sandwich-type immunoassays with ICP-MS detection* for biological analysis. Multiplex measurement of serum biomarkers, alpha-fetoprotein (AFP), neuron specific enolase (NSE) and C-reactive protein (CRP), was achieved *via* Cs-doped multicore magnetic NPs immobilised with polyclonal antibodies to extract the biomarkers from the sample and three different metal (Au, Cd, Y)/dye-doped SiNPs immobilised with monoclonal antibodies for detection by ICP-MS and visualisation by fluorescence imaging.[56] The design had several advantages over previously reported work, including Cs within the magnetic NP core to allow ratiometric measurement in ICP-MS and incorporation of different metal tags whilst maintaining an NP probe size <90 nm, which is required for good extraction efficiency and reproducibility. Slightly superior LODs to those typically seen with automated immunoassay methodologies were achieved (0.37, 0.36 and 77 ng mL^{-1} for AFP, NSE and CRP respectively). Linearity was satisfactory up to 100 ng mL^{-1} for AFP/NSE and up to 10 000 ng mL^{-1} for CRP. Recoveries from spiked samples were 83% to 125%. Although no prior sample preparation was required, assay run times were long (>4 h) compared with automated immunoassays. Furthermore, expansion to include more metal tags, while maintaining a small probe size, may be a challenge. A similar approach involved a novel multifunctional NP probe for both cell counting and multimodal imaging of cancer cells.[57] The probe consisted of an antibody to bind anti-EPCAM antibody-labelled cells, a fluorescent dye moiety for down-conversion fluorescence and an up-conversion NP tag, incorporating ^{89}Y, for luminescence and ICP-MS quantification. Under optimised conditions, excellent linearity (R^2 of 0.9955 for 400 to 30 000 HepG2 cells) and sensitivity was demonstrated with an LOD of 100 HepG2 cells and RSD of 7.1% at 1000 HepG2 cells. *Simple metal tags* may also be utilised to label and detect biomolecules and He *et al.*[58] reported use of Eu^{3+} chelate labelling to determine trace concentrations of the paralytic toxin, saxitoxin, in mussels using CE-ICP-MS with a run time of 13 minutes. Mussel sample preparation involved vacuum freeze drying, pulverisation and extraction of saxitoxin into DMSO before Eu^{3+} labelling *via* the coupler, pentetic acid. The merits of the described method were strong anti-interference ability, good

stability and very good sensitivity with an LOD of 3.8 nmol L^{-1} and RSDs <7%. Recoveries from spiked mussels were 93–100%.

Dual analysis, combining accurate quantification by ICP-MS with the identification capabilities of molecular MS, offers versatility for both biological and food analysis. The combined application of HILIC-ICP-MS/ESI-FT-MS and SEC-ICP-MS/ESI-FT-MS to large scale detection of >50 metal complexes in green pea plant fluids was reported by Flis *et al.*[59] Data were collected using two chromatographic systems with different mobile phase conditions and in positive and negative ionisation modes to enable confirmation of the findings and elimination of minor artefacts. The column recovery of metal complexes was 60% to 90%. Interestingly for multi-elemental ICP-MS analysis, H_2 reaction gas rather than He collision gas was employed. Several isotopes were monitored by ICP-MS to improve quantification accuracy and use of HR-mode ESI-FT-MS enabled isobaric interferences to be overcome. Inclusion of ICP-MS afforded increased sensitivity and obviated the need for individual species standards for quantification, facilitating identification of previously unreported species.

Last year saw the application of *ICP-QQQMS* to halide analysis in blood plasma and this year the technique has been used to determine F in tea.[60] Due to its low IP, F was converted to BaF^+ in the plasma before reaction with gas mixture 10 : 90 NH_3 : He at 8.0 mL min^{-1} to form $BaF(NH_3)_3^+$, which was monitored at *m*/*z* 157 → 208. The mass shift strategy avoided Gd interference although the relevance of this in tea is questionable. The RF power, which affects the competition between BaO and BaF in the plasma, was optimised to 1500 W. An LOD of 0.022 μg mL^{-1} was achieved and good agreement with certified values for food SRMs was observed. In 13 branded tea samples, F concentrations (39.2 to 93.2 μg mL^{-1}) agreed well with those obtained by ISE. Utilisation of ICP-QQQ-MS with O_2 reaction gas for high sensitivity As analysis, thus avoiding interference on *m*/*z* 75, was this year extended to food and beverage matrices. Pinheiro *et al.*[61] measured total As in fruit juices, preparing the samples by closed vessel microwave assisted digestion and achieving an LOD of 0.03 μg L^{-1} with recoveries ranging from 88% to 109%. Another group developed a fast As speciation method (<2 min) for DMA, MMA and iAs in wine and rice,[62] which featured a short narrow bore 5 μm column and decreased mobile phase flow rate to reduce sample dilution and increase transport efficiency. Consideration was given to mitigating the well-known C-enhancement effect in the EtOH matrix which was achieved through a low sample injection volume (5 μL) and addition of 3% MeOH to the mobile phase. Prior oxidation of As^{III} to As^V by H_2O_2 facilitated faster separation and improved S/N for As^V while pre-column injection of AB internal standard increased accuracy through drift correction. The LODs achieved were 0.022, 0.018 and 0.026 μg kg^{-1} for iAs, DMA and MMA respectively. Results were within 13% of the reference method target in wine and spiked recoveries were 93 to 123% in rice.

The *combination of ICP-QQQ-MS and dual analysis* was applied to the determination of arsenolipids adsorbed onto bentonite,[63] a mineral used to reduce contaminants during production of commercial fish oil. A clean-up procedure to remove phospholipids, which cause ion suppression in ESI-MS, consisted of sequential solvent extraction before each fraction was run on a normal phase Si-gel column with an increasingly polar eluent. Quantification and identification of arsenolipids was accomplished by RP-HPLC followed by ICP-QQQ-MS against a DMA^V standard and Ge internal standard, and HR-ESI-MS. Clean-up column recovery was 89 to 95% and total mass recovery was 88%, indicating minimal loss of As during the extraction, clean up and speciation steps. Five new arsenolipids were identified including three As-containing medium chain fatty acids, thought to be degradation species resulting from the clean-up procedure. In the more exotic matrix of snake venom, Calderón-Celis *et al.*[64] described the μHPLC separation of intact S-containing proteins with quantification using ICP-QQQ-MS and ^{32}S : ^{34}S ID and identification by ESI-QTOF-MS. The approach required only one ^{34}S-containing standard (added continuously post-column) to quantify all cysteine- and methionine-containing proteins with known S:protein stoichiometry. Samples were diluted and centrifuged prior to separation by RP-μHPLC with gradient elution consisting of 0.2% aqueous formic acid and ACN. Addition of BOC-methionine internal standard, significantly reduced the complexity of the ID equations rendering correction of post-column flow and a mass discrimination factor unnecessary. Total protein recovery was 92.6% to 97.4%. The LODs achieved for ICP-QQQ-MS were 15 to 25 fmol. When applied to proteomic analysis of venom from three snakes, results were in fairly good agreement with previously reported work with some discrepancies for minor proteins.

Another report making use of *IDMS techniques* presented the development of a high precision candidate reference method for speciation and quantification of metalloprotein, Cu–Zn–superoxide dismutase (SOD1), *via* Cu detection in red cells, using species-specific double and triple IDMS with strong anion exchange HPLC-ICP-MS.[65] The isotope enriched spike, prepared from a commercially available SOD1 calibration standard and ^{65}Cu and ^{67}Zn enriched standard solutions, was added to the sample prior to preparation and separation to compensate for any losses or changes during these processes. While double IDMS used a reference spike blend with a 1 : 1 ^{65}Cu : ^{63}Cu ratio and obviated the need to know the purity of the species specific spike used, the triple IDMS involved two reference spike blends with ^{65}Cu : ^{63}Cu ratios of 0.9 and 1.1 and did not require the isotopic composition of the spike to be determined, although at the cost of longer measurement times. The calculated mass fractions of SOD1 were in good agreement for double and triple IDMS; 63.94 ± 0.93 μg g^{-1} and 64.02 ± 0.96 μg g^{-1} respectively. Excellent precision was demonstrated with an expanded uncertainty of ≤1.50% $k = 2$, 95% CL).

Last year, an improved procedure for the direct isotopic ratio analysis of Fe in whole blood was discussed. A report this year[38] described the development of a Cu isolation procedure in serum, prior to MC-ICP-MS analysis, to reduce concentrations of matrix elements that have an effect on instrumental mass discrimination. Following acid digestion of serum, the new procedure consisted of removal of alkali and alkaline earth metals *via* 1 mL Chelex-100 chelating ion exchange resin before

further purification of the Cu fraction using 250 μL AGMP1 strong anion exchange resin. This was compared to the conventional sample preparation. Advantages of the modified procedure were decreased volumes of high purity acid, cost and time required and lower blanks. Using standards of known isotopic composition and serum RMs, no statistically significant differences were found between δ^{65}Cu values obtained by the proposed and conventional procedures. Use of the propriety jet interface system, rather than standard MC-ICP-MS interface cones led to superior precision for δ^{65}Cu (0.01‰ to 0.03‰) and reduced effects of instrumental mass discrimination for aqueous standard solutions but a stronger influence of matrix elements on Cu isotope ratios was noted.

4.2 Atomic absorption spectrometry

There is little that is new to highlight from the last year. The main area of activity appears to be *applications exploiting HR-CS-ETAAS* with methods that are reported to be simple, rapid and sensitive. Ajtony *et al.*[66] measured concentrations of Cu in Hungarian distilled alcoholic drinks. Samples were injected and analysed without any modifier. With internal standards (Cr, Fe or Rh) and a fast heating programme, results were achieved within 1.5 min. An LOD of 0.03 mg L^{-1} was cited and the recovery of added Cu was 100.9 ± 8.5%. Measurements of Cu and Mn concentrations in infant formula were described by Gamela and co-workers.[67] Samples were ground and homogenised and sample masses of 3.0 mg and 1.0 mg for Cu and Mn, respectively were added to the furnace. As reported by Ajtony *et al.*,[66] no modifier was necessary. A pyrolysis temperature of 1300 °C was applied, followed by atomisation temperatures of 2300 °C for Cu and 2100 °C for Mn, respectively. Results from the analysis of a CRM NIST SRM 1568a rice flour were consistent with the certified concentrations. In real samples, concentrations of Cu were 1.3–6.8 μg g^{-1} and 0.7–17.2 μg g^{-1} for Mn. The matrix type of choice for de Andrade *et al.*[68] was meat. Using CRMs to validate methods to measure concentrations of Mn, Ni and Rb, optimum temperatures for pyrolysis and atomisation were found for each element. Spectral interferences on Ni at 231.096 nm from SiO and PO, required correction using least-squares background correction using Solid standards proved to be essential for quantitation of Ni and Rb but aqueous calibrants could be used for Mn. Analysis of CRMs gave results in agreement with the certified values, and with LODs of 0.005, 0.002 and 0.1 μg g^{-1} for Mn, Ni and Rb, respectively, the method was suitable for analysis of meat samples.

Those with personal experience of *measuring Zn concentrations by ETAAS* will be well aware of problems associated with contamination of equipment and reagents and interfering species. Concentrations in plasma are usually high enough to be determined by FAAS or other techniques but where the available sample volume is very small, such as from young babies, ETAAS may be required. The work by Stevens *et al.*[69] utilised two chemical modifiers, a Mg/Pd mixture combined with 1% (w/v) EDTA, which allowed a pyrolysis temperature of 1000 °C for effective removal of the Cl^- interference. Samples were and standards were simply diluted 20-fold using 0.05% (v/v) Antifoam B Emulsion and Triton-X-100 prior to measurement. Recovery studies, comparison with ICP-MS and FAAS methods and analysis of a commercial RM all confirmed the accuracy of results.

An original application of FAAS was reported by Altunay *et al.*[70] who developed *an indirect method to measure concentrations of histamine* in fish, dairy products and alcoholic beverages. Histamine forms a complex with Fe(III) and 2′,4′,5′,7′-tetrabromofluorescein (eosin) at pH 4.5 which can be extracted into the micellar phase of polyethylene glycol dodecyl ether (Brij 35). Ultrasonic assisted CPE was used to separate and preconcentrate the histamine from the sample matrices, followed by FAAS measurement of the associated Fe. The optimum reagent concentrations and other conditions were evaluated and the procedure achieved an LOD of 0.25 μg L^{-1}.

4.3 Atomic emission spectrometry and laser induced breakdown spectroscopy

Two publications refer to *novel GD-AES systems*. Jamroz *et al.*[71] used a liquid drop anode d.c. atmospheric pressure GD-AES system to determine concentrations of Cd in biological CRMs. This device included a solid pin type tungsten cathode and a liquid drop placed on a graphite disc anode. With a 50 μL sample drop a linear range of 1–1000 μg L^{-1} was obtained and the LOD was 0.20–0.40 μg L^{-1}. The influences of organic compounds, easily ionised elements and Al, Cu, Fe, Mn and Zn on atomization and emission were evaluated. The recoveries of Cd in the CRMs were 96.3–99.6%. A very different construction was developed by Yu *et al.*[72] who prepared a liquid cathode GD-AE spectrometer to measure concentrations of Ca, K, Mg, Na and Zn in tap water and mineral water. The plasma was established between a needle-like Pt anode and electrolyte around a quartz capillary cathode. The contributions of the supporting electrolyte, discharge voltage and organic additives to the emission intensity were evaluated. With HNO_3 (pH = 1) as supporting electrolyte, 0.15% formic acid and 650 V discharge voltage the LODs were equivalent to those achieved with closed-type electrolyte-cathode discharge AES. The authors suggested that liquid cathode GD-AES offers low cost portable equipment with real time and online analyses.

Photochemical vapour generation for ICP-AES featured in a novel application in which a volatile Co species was generated from acid digested biological tissues. In this work de Jesus *et al.*[73] took Co^{2+} solutions in a pH 3.3 medium of 50% formic acid for exposure to deep UV (254 and 185 nm) radiation generated within a 19 W flow-through low pressure mercury discharge lamp. A phase separation device allowed the analyte vapour to be transported to the ICP-AES system for detection at the 238.892 nm emission line. Investigations of the performance indicated that in a continuous mode, with an irradiation time of 10 s, the generation efficiency was 42% and the LOD was 0.4 μg L^{-1}. Matrix interferences from some digested samples required longer irradiation times, additional dilution and standard additions calibration to give accurate results. A second application with photochemical vapour generation was reported by Covaci *et al.*[74] Seafood samples were prepared using

the procedure recommended in the JRC Technical Report of the European Commission for the determination of MeHg. The MeHg extracted from samples was directed to a flow injection UV photo-reduction system to generate Hg vapour for AE at the 253.652 nm line with a low power/Ar consumption plasma microtorch. The LOD and LOQ, 2 μg kg^{-1} and 6 μg kg^{-1}, respectively and RSD of 2.8% meet the requirement of the European legislation for this application. Analysis of CRMs confirmed the trueness of results.

The concern around metal-on-metal hip replacements has been discussed in recent Updates with a focus on Co and Cr but other elements such as Ti are present in the prostheses and may be relevant to the problems experienced by some patients. Titanium cannot be easily determined by Q-ICP-MS due to interferences from Ca isotopes. Therefore, Harrington *et al.*[75] developed and validated a simple method to measure concentrations of *Ti in whole blood, serum and hip fluid by ICP-OES* using the Ti 336.1 nm emission line and an Y internal standard. Increased levels were measured in samples from patients where Ti was a component in the femoral stem or total hip replacement prostheses.

Santos *et al.*[76] reported an *ETV-ICP-OES* method said to give results for eight elements in powdered medicinal plants in less than 5 minutes, including sample preparation time. The optimised procedure used the rather unusual choice of Freon R12 (CCl_2F_2) as the modifier and temperatures of 300 and 1800 °C for pyrolysis and vaporisation, respectively. Standard additions calibration was necessary to compensate for residual matrix effects. The LODs for As, Cd, Cr, Cu, Mn, Ni, Pb and Zn were from 0.01 to 0.48 μg g^{-1}. Results obtained from the analysis of two NIST CRMs were in good agreement with the certified values.

Developments with *elemental imaging* using MS and X-ray spectrometry are discussed in Section 6.2 but Thyssen *et al.*[77] propose that LA-ICP-OES is an alternative technique for bio-imaging of the easily excited alkali and alkali earth elements.

A number of publications have highlighted LIBS as a useful system for rapid analysis in food and beverage products for a variety of purposes. Casado-Gavalda *et al.*[78] described the *application of LIBS to detect offal adulteration in beef*. The concentration of Cu was used as an indicator because offal can contain over 100-times higher levels than in meat. Samples of minced beef and liver were dried, homogenised into powder before mixing together and pressed into pellets at different ratios to generate the in-house calibration standards. These were characterised by ETAAS and the values incorporated into the PLS regression calibration model using the LIBS spectral data. Two separate sample sets were employed to train the system, with a third independent set applied as the test, which achieved a high R_{cv}^2 of 0.85 which was considered reasonable for LIBS. Furthermore, the spatial homogeneity of the pellets was assessed by taking 100 spots across the surface. Two additional sample pellets were produced containing sections with two different ratios of beef : liver. A visual inspection of the maps generated showed a fair level of homogeneity in the calibrants and some regional distinction in the multi-surface pellets, though no formal statistical analysis was presented. Overall, the method did demonstrate the potential to identify offal adulteration in meat. Chicken breast fillets were the subject of a study by Abdel-Salam and co-workers[79] who investigated the feasibility of using LIBS and LIF as a rapid and cost-effective system to identify meat spoilage. Samples were analysed by LIBS for the cyanide and carbon molecular bands to monitor protein content and the ratio of 'ionic to atomic' spectral lines for Mg and Fe as an indicator of meat tenderness. The LIF data showed an inverse relationship between the fluorescence band intensity and the storage time. After comparing the results against a conventional meat analyser, the authors concluded that both LIBS and LIF were promising techniques to detect degradation in the meat processing industry. Augusto *et al.*[80] utilised LIBS for the direct determination of Ca, K and Mg in milk powders and dietary supplements. The calibration strategies relied on additional measurements by ICP-OES after acid digestion for the PLS regression calibration. The method accuracy ranged between 60% to 168% for Ca, 77% to 152% for K and 76% to 131% for Mg. Considering the LIBS approach could achieve a throughput of one sample per minute with no preparation, the results were encouraging.

Typically, the *direct analysis of samples with high moisture content or liquids/solutions by LIBS* can suffer significant problems but a number of publications have attempted to solve this issue. Moncayo *et al.*[81] developed an approach to classify red wines based on the 'protected designation of origin' region. To minimise the difficulties associated with aqueous samples, the group presented a novel and simple preparation procedure which converted the liquid wine into a solid by generating a dry collagen gel. With the use of neural networks, a model was designed and tested using genuine and 'fake' wines to successfully assign the correct categories. The method was simple, quick and could be used for authenticity purposes and quality control screening. Pasquini and Farias Filho[82] described an instrumental development of LIBS which incorporated a ring-oven as another technique for liquid-to-solid conversion and as an online pre-concentration approach. In this work, further improvements were made to the ring-oven set-up and inclusion of an internal standard (Li) enabled correction for problems associated with repeatability and laser pulses missing the target. Once optimised, it was used to determine Cu concentrations in samples of cachaça (a Brazilian spirit derived from sugarcane juice). The LIBS method achieved an LOD and LOQ of 0.3 and 1.0 mg L^{-1} respectively. It was compared with AAS as the reference method and in general, the results obtained were in good agreement, given the reported RSDs, with the exception of one sample which was approximately 44% higher by LIBS. The authors performed further experiments which demonstrated changes in the slope of the calibration curve for the ring-oven/LIBS method in the presence of sugar. Overall, the study showed that LIBS with integrated sample preparation and pre-concentration had potential as a fast screening technique (6 minutes per sample). Hedwig *et al.*[83] described the combination of ps-LIBS with a vacuum sample chamber pressurised at 2 kPa with He which was shown to significantly improve emission intensities in plant materials when compared against ambient air. With the optimised setup,

slices of carrot and meatballs were spiked with Pb and B to assess the emission characteristics in samples with a water content of approximately 15–20%. The LOD was estimated at 100 ppb for Pb and 200 ppb B which was respectable given the direct analytical approach.

A biological application of *fs-LIBS to detect Hg migration from amalgam in teeth* was presented by *Bello et al.*[84] who optimised the instrumental parameters to detect Hg plus Ag, Ca, Cu, Mg and Sn as markers of the amalgam, tooth and interface regions. Deciduous and permanent teeth were also compared and an assessment of elemental penetration depth was calculated. The fs-LIBS spectra for each tooth section showed expected behaviours where Ag, Cu, Hg and Sn were at the highest intensity in the amalgam which decreased towards the tooth whereas Ca and Mg on the other hand were only observed in the tooth and interface areas. A difference in Hg penetration depth was found between deciduous and permanent teeth (157 ± 7 μm *versus* 173 $\pm$ 6 μm respectively) which could be a factor of the residence time of the amalgam, however the age of the restorations was not known. Considering the regions analysed, the authors hypothesised that the diffusion mechanism was linked to liquid transport through the dentinal tubules.

4.4 Vapour generation procedures and atomic fluorescence spectrometry

Compared with the work reviewed in our recent Updates, publications during the last year show evidence of originality in both analytical design and in application. In Section 4.3, above, *photochemical vaporisation* for AES was described as applied to determination of Co in biological samples and MeHg in fish.[73,74] Potes *et al.*[85] also exploited photochemical vaporisation with ETAAS to measure total Hg in fish, following dissolution in TMAH. The experimental conditions were systematically optimised and, from a sample weight of 0.1 g, the LOD was 0.03 μg g^{-1}. Compared to CV generation, the photochemical system produced a vaporisation efficiency of 85%. Analysis of three CRMs confirmed the method accuracy.

Two other procedures for *Hg vapour generation followed by AAS* were reported. Sabouri and Nouroozi[86] described an online method to directly determine iHg and MeHg in urine determined Hg in urine. An FI system was used which included an Fe^{3+} catalyst to ensure equal vaporisation efficiencies for MeHg and iHg, enabling calibration with iHg only. Concentrations of Hg in two CRMs were determined at 107.7% and 97.3% of the certified values and spikes of Hg^{2+} and MeHg were recovered in the range of 93.4% to 104.5%. A sample throughput of 108 h^{-1} was reported. Total Hg and MeHg in seafood were measured by Yoshimoto *et al.*[87] using IBMK to remove fat, leaving the Hg in the aqueous phase. The MeHg was then extracted from an aliquot of the aqueous phase with HBr, $CuCl_2$ and toluene, and back-extracted into an L-cysteine–sodium acetate solution. Heating-vaporisation AAS was used to detect and quantify the concentration of Hg. Analysis of CRMs demonstrated accuracy of the procedure. The approach was applied to determine the level and ratios of total Hg and MeHg in glands of squid and sea urchins. Most of the Hg in squid was MeHg whereas in sea urchin it represented less than 4% of the total concentration.

Atomic fluorescence spectrometry was used in a number of different applications. Continuing with the theme of Hg, the procedure to prepare small amounts of biological samples for determination by glow-discharge CV-AFS[35] was described in Section 3.2.1. A non-chromatographic method to determine four As species by modified graphite electrode-based electrolytic HG-AFS was developed by Yang *et al.*[88] The electrode was modified with either L-cysteine or glutathione and, depending on the applied current, As^{III}, As^{V}, MMA and total As were selectively measured. Zeng *et al.*[89] were able to generate volatile species of Mn through reduction of acidified analyte solutions in the presence of 0.1% APDC and 0.1% 1-butyl-3-methylimidazolium hexafluorophosphate with 2.0% KBH_4 and 0.1% phenanthroline. Efficiency of vaporisation was calculated to be 44%. With optimised parameters the LOD was 1.5 ng mL^{-1}. The method was successfully applied to the determination of Mn in water sample and environmental CRMs. Electrothermal vaporisation from a quartz furnace was introduced by Shang *et al.*[90] to determine Pb in foods with detection by AFS. Temperatures for ashing and vaporisation were optimised to remove matrix interferences and the accuracy of the method was assessed by analysis of CRMs.

4.5 X-ray spectrometry

A comprehensive review of recent advances in X-ray spectrometry[2] accompanies this Update and includes applications with clinical and biological materials, foods and beverages. Imaging applications of X-ray spectrometry are described separately in Section 6.2 below.

The past year has shown an overall reduction in the number of noteworthy X-ray spectrometry papers in comparison to the previous Update.[1] However, several publications have highlighted the use of *X-ray based techniques for food analysis*. Hanley *et al.*[91] reported a rapid screening method with XRF for total Se determination in dietary supplements. Both solid and liquid formulations were tested which required different calibrations to account for the matrix effect: serial dilutions of a standard Se solution for the liquid samples and the CRM SELM-1 was mixed gravimetrically with cellulose to produce the solid calibrants. Additionally, the authors developed an approach for Se speciation using direct analysis in real time high resolution accurate mass–mass spectrometry (DART-HRAM-MS). Both total and species data were compared against conventional ICP-MS and HPLC-ICP-MS. The XRF method had an LOD and LOQ of 4 μg g^{-1} and 30 μg g^{-1} respectively, which is more than adequate for supplement testing, with good agreement was observed against the ICP-MS data when a quadratic fit calibration equation was used for XRF. Similarly, the DART-HRAM-MS results produced comparable values to HPLC-ICP-MS for non-protein bound SeMet and MeSeCys, achieving an LOD of 100 μg Se species per capsule. An attempt was made to detect iSe but practical issues such as sensitivity and carry-over prevented this. However, given that no sample preparation was required and the fast measurement times (40 minutes for both methods), the

combination of XRF and DART-HRAM-MS offered significantly increased throughput with suitable accuracy levels. Gerenyi and co-workers[92] published an interesting application of XANES to investigate the uptake of As in cucumbers. Liquid nitrogen 'steam' was used to cryogenically preserve the vegetable which enabled the researchers to determine the As oxidation state *in vivo* to understand the metabolic pathways of As.

The use of *X-ray techniques for clinical applications*, particularly for *in vivo* bone measurements, was the focus of several papers. Groskopf *et al.*[93] prepared bone and skin phantoms doped with As and Pb to evaluate SR-XRF against portable XRF. The thickness of the skin layer was also considered. Although the LODs using SR were better, the study demonstrated similar results for both techniques, adding evidence to support the use of portable XRF systems as *in vivo* measurement devices. Specht and co-workers[94] described a theoretical model using Monte Carlo simulations to assess the feasibility of a portable XRF device with a high-energy X-ray tube and room temperature detector, for the measurement of Pb in bone. The results were compared with experimental data and good agreement was observed. Byrnes and Bush[95] evaluated the ability of portable XRF for forensic bone analysis. Factors, such as bone depth, were investigated using equine bone of known thickness. Historic specimens were then tested before and after sanding the periosteal surface to determine any changes in the XRF response due to potential diagenesis. It was concluded that portable XRF is a convenient tool for onsite analysis but still has some limitations. Huszank *et al.*[96] published a study utilising PIXE and PIGE for the direct determination of various elements (Br, Ca, Cl, Cu, Fe, K, Na, P, S and Zn) in liquid blood samples. The combination of techniques using the 'in air' microbeam configuration enabled the measurement of small sample volumes (~10 μL) in serum, plasma and whole blood with no preparation. The authors suggested that the approach was suitable for routine use in the ppm range but added that levels closer to 1 ppm required longer measurement times with poorer accuracy.

A paper by Sanchez-Cano *et al.*[97] described the use of a new *nanoprobe beamline for SR-XRF to investigate the cellular distribution of a new osmium-based candidate cancer drug*. Human ovarian carcinoma cells A2870 were exposed to 1 μM of the Os complex, purported to be 49 times more potent than cisplatin, for 24 h before fixation with paraformaldehyde. The SR-XRF beamline was 27 × 37 nm^2, scanned at step sizes of either 50 × 50 nm^2 or 20 × 20 nm^2 and a dwell time of 50 ms. Detailed image maps were generated for Ca, Os, P and Zn which allowed the researchers to gain insight into the mechanism of action. Localisation of Os in the mitochondria effected reactive oxygen species which appeared to induce Ca release from the endoplasmic reticulum, a signalling event for cell death. The study highlighted important and crucial findings in the search for new cancer therapies.

5. Nanomaterials

As mentioned in Section 1, the *applications of nanomaterials* are rapidly increasing with respect to the topics that are relevant to this Update. This section briefly considers publications that feature nanomaterials in the context of exposure and absorption, toxicity, as reagents in analytical methods and analysis or characterisation of materials.

Pulmonary exposure to NPs is of particular interest. Gate *et al.*[98] measured Ti concentrations in young and elderly rats by ICP-MS, following exposure to 10 mg m^{-3} aerosols for 6 h day^{-1}, 5 days $week^{-1}$ for 4 weeks. Titanium in the lung slowly cleared post-exposure and was found in the spleen, and liver with higher concentrations in the elderly animals. No increase in Ti was detected in blood, kidney or brain. Pujalte *et al.*[99] studied rats exposed to 15 mg m^{-3} aerosols, for just 6 h. Peak concentrations in the lung were found at 48 h and decreased over 14 days. Titanium was present in blood, lymph nodes, liver, kidney and spleen. Measurable amounts were also determined in olfactory organs and brain. Large amounts of Ti were present in faeces suggesting that inhaled NPs were eliminated mainly by mucociliary clearance. These two reports indicate that absorption and further metabolism is complex and further work is required to understand the implication of exposure to TiNPs. Cerium oxide NPs in diesel fuel additives can ultimately lead to human inhalation. The emitted NPs undergo an aging process by interaction with other airborne pollutants and this may influence the biodistribution after inhalation. Therefore, Li and colleagues[100] investigated inhalation exposure of Sprague Dawley rats to combustion-generated CeO_2NPs. Test samples were aged in a chamber representing ambient urban air conditions, with UV lights. Exposure was to freshly emitted or aged CeO_2NPs for 15 min, 24 h, and 7 days followed by measurement of Ce in the blood, lungs, gastrointestinal tract, liver, spleen, kidneys, heart, brain, olfactory bulb, urine, and faeces. Cerium was found in the lungs and faeces, with extrapulmonary organs contributing less than 4% to the recovery rate at 24 h post exposure. No significant differences were found between fresh and aged CeO_2NPs. The findings from all of these studies of Ce and Ti in olfactory organs and brain are similar to observations with Hg vapour and may indicate translocation *via* neural pathways.

Two reports refer to *metabolism of NPs during pregnancy*. Austin *et al.*[101] examined the distribution of Ag in pregnant mice and embryos/foetuses following intravenous injections of 10 nm AgNPs or 66 mg Ag/mouse on gestation days 7, 8 and 9. Highest concentrations of Ag were found in maternal liver, spleen and visceral yolk sac. Levels in the yolk sac of the $AgNO_3$ treated mice were twice those of the NP exposed animals but there were no significant differences in other tissues examined. One or more embryos from eight of the ten AgNP-treated mice were small for their age, an effect that was seen in embryos from only one mouse in the control group. Silver accumulation in embryos/foetuses was negligible. Muoth *et al.*[102] determined the uptake of AuNPs into human placental co-culture microtissues in the context of NPs drug carriers. Uptake was found to be greater with smaller (3–4 nm) or sodium carboxylate-modified AuNPs than with larger (13–14 nm) or PEGylate AuNPs, for which there was minimal passage through the trophoblast barrier layer. The authors suggest that the effectiveness of

AuNP-drug carriers can be optimised by tailoring their properties.

A number of *investigations having relevance to intestinal absorption* were reported in the last year. Gallocchio *et al.*[51] administered AgNPs to hens and showed that Ag accumulated in liver and egg yolk. Single particle ICP-MS (spICP-MS) and SEM-EDX spectrometry results that 5–10% of the Ag in liver was as the NP form. In an *in vitro* experiment, Ramos *et al.*[50] measured Ag after samples of chicken meat containing 40 nm AgNPs were treated with either saliva, gastric or intestinal fluids. Single particle ICP-MS indicated that 13% of the AgNPs would be available to the intestinal cells while up to 44% of the initial material would be in bioaccessible dissolved forms. Previous Updates have noted work that has shown transfer of metals from food contact materials, containers and cooking utensils into food products. Some of these studies refer specifically to AgNPs incorporated into containers *etc.* because of their antimicrobial properties. Williams *et al.*[103] pointed out that AgNPs may, therefore become available for intestinal exposure with potential implications on health of consumers. These workers assessed the effects of AgNPs of different sizes and doses T84 human colonic epithelial cells. Uptake into cells was demonstrated by ICP-MS analysis and TEM, together with perturbation of parameters indicative of cell function. The smallest AgNPs (10 nm) had the greatest effects.

There is considerable interest in the *pharmacological applications of nanomaterials*. Escudero-Francos *et al.*[104] used a variety of techniques, including ICP-MS to assess the *in vitro* uptake into fibroblasts and the *in vivo* biodistribution of AuNPs functionalised into nanoclusters with mercaptoundecanoic acid (MUA), GSH or BSA. The lack of toxicity and the preferential tissue uptake of MAU, GSH and BSA Au-nanoclusters into brain, kidney, liver and spleen, respectively point to potential organ-specific carriers of drugs. In a similar study, Mahmoud and colleagues[105] assessed Au nanorods (AuNR) functionalised with neutral, anionic, cationic, and hydrophobic ligands. Using ICP-OES and LA-ICP-MS, accumulation into hair follicles and other skin compartments of human skin sheets was measured. The lipophilic properties of hair follicles enhanced the accumulation of hydrophobic polystyrene (PS)–AuNR into hair follicles while neutral polyethylene glycol (PEG)–AuNR were distributed into all skin compartments, especially the dermis. Charged AuNR showed a negligible penetration into any of the skin layers. These properties could be exploited for targeted skin disease treatment and transdermal administration of drugs. Auoxo3 is a cytotoxic Au^{III} compound which exhibits promising anticancer activity. When encapsulated in a ferritin nanocage there is significantly less damage to non-tumour cells.[106]

Despite the many positive features associated with nanomaterials, *acute exposure studies with TiO_2 have shown that there can be harmful consequences.* In the work reported by Armand *et al.*[107] possible toxicity from long-term exposure to low concentrations of TiO_2NPs was assessed using A549 alveolar epithelial cells. Genotoxicity was determined by alkaline and Fpg-modified comet assay, immunostaining of 53BP1 foci and the cytokinesis-blocked micronucleus assay and the impact of a subsequent exposure of these cells to the alkylating agent methyl methanesulfonate. Cytotoxicity and intracellular accumulation were determined using conventional tests and ICP-MS. The results showed that while long-term exposure to TiO_2NPs does not affect cell viability, it does cause DNA damage, particularly oxidative disruption to DNA and increased 53BP1 foci counts. These results correlated with increased intracellular accumulation of NPs. Following intra-venous injections of Tween® 20-gold AuNP conjugates to mice, Berce *et al.*[108] determined haematological parameters, Au concentrations in tissues and the appearance of bone marrow cells. The results indicated accumulation of Au in the bladder and bone marrow, proliferation of white blood cells and platelets and liver toxicity. From this experiment it was uncertain whether there was simply a reaction to the presence of Au or if a severe haematological condition could later develop. The authors warned that the potential use of AuNPs in cancer therapy must be evaluated against possible harm.

Nanomaterials feature prominently in new developments for analytical procedures. A review by Karadjova *et al.*[14] summarised the different materials that have been used for *elemental speciation.* The authors considered size, surface to volume ratio and chemical reactivity and how the properties were exploited for the analysis of environmental, food and biological samples. The work of Zhu *et al.*[109] using Fe_3O_4@SiO_2@gamma-mercaptopropyltrimethoxysilane magnetic NPs to successfully speciate Hg in samples of water and fish is described in Section 6.1 Metallomics, below. In the same vein, Abbaszadeh and Tadjarodi[110] developed what they termed a magnetic metal–organic framework for As speciatiation in water, rice and tuna samples.

To *extract and concentrate iHg from samples of water and CSF*, Hsu *et al.*[37] also exploited magnetic NPs. The SPE procedure employed NPs with a Fe_3O_4 shell, Au core and an L-cysteine functional group. Unlike conventional SPE methods, desorption of Hg for measurement by ICP-MS, was not necessary. A novel sorbent was developed by Alpdogan *et al.*[111] to measure Cd, Cr, Cu, Mn, Ni and Pb from milk, with an impressive preconcentration factor of 600. These workers used a column containing TiO_2NPs, functionalised with *Aspergillus niger*. The selected elements were retained at pH 6.0, eluted with 0.5 mol L^{-1} HNO_3, and determined by FAAS.

In recent years we have seen a small number of *publications describing immunoassays* in which the final analytical step is the measurement of a metal label by ICP-MS. Two publications report original analytical approaches in which NPs have a role. Ko and Lim[56] synthesised three metal/dye-doped silica NPs as probes for simultaneous detection of the disease markers C-reactive protein, alpha-fetoprotein and neuron-specific enolase. This sandwich immunoassay also used Cs-doped multicore magnetic NPs for magnetic extraction of the analytes and quantification using ICP-MS. No sample treatment was necessary prior to the extraction and the sensitive method

provided short analysis time and convenience for the determination of these biomarkers. Detection limits ranged from 0.35 ng mL^{-1} to 77 ng mL^{-1}. An immunoassay for cancer cells, counting and imaging with the aid of a multifunctional probe, was described by Yang *et al.*[57] The probe consisted of a recognition unit of goat anti-mouse IgG to label the anti-EpCAM antibody attached cells, a fluorescent dye (Cy3) moiety for fluorescence imaging and upconversion NPs tag for both ICP-MS quantification and imaging of cancer cells. Excellent linearity and sensitivity were achieved due to the signal amplification effect of the NPs.

Signal amplification due to inclusion of NPs in assays was also discussed in a review of laser desorption/ionisation coupled with MS, by Unnikrishnan *et al.*[112] Nanomaterials, such as AuNPs, with high photoabsorption, photothermal conversion, and heat-transfer efficiency, reduce the interference of matrix molecules, and improve the reproducibility and sensitivity. Monitoring the ligand ions and Au cluster ions amplifies the mass spectral signals and allows analysis of macromolecules with minimum errors.

With the increasing application of NPs in a wide range of manufacturing and other sectors, *analysis of NPs in clinical, foods and environmental samples* is required. Two articles reviewed approaches to the analysis of nanomaterials. De la Calle *et al.*[113] discussed the techniques for extraction and preconcentration from the sample matrix, separation of NPs from ionic species and larger particulates and size fractionation. Applications to biological tissues, food, environmental samples, cosmetics and other consumer products were described with discussion of the advantages and inconveniences of the procedures mentioned. In their review of analysis of nanomaterials, Montano *et al.*[15] referred specifically to the technique of spICP-MS. The extensive discussion included advances in data acquisition, signal processing and different mass analysers. The key features for quantitative analysis are explained with examples of analysis of increasingly complex environmental and biological samples. A method with SEC and ICP-MS was described by Zhou and colleague[114] to characterise particle size, mass and composition of trace NPs in serum and water. Complete elution from the column of different-sized NPs was achieved using a mobile phase with a relatively high ionic strength, 2% FL-70 and 2 mM $Na_2S_2O_3$. The size distribution of NPs agreed closely with that obtained using TEM. Donovan *et al.*[53] reported the measurement of Ce- and Zn-containing NPs in surface and drinking water by spICP-MS. Laboratory experiments with river water were conducted in which sequential treatment by lime softening, alum coagulation, powdered activated carbon sorption and disinfection by free chlorine, were applied. The results showed that most of the CeNPs were captured during lime softening and that ZnNPs were progressively removed by the additional treatments. Analysis of real source and drinking water samples showed at least 60%, and in most cases >95%, of NPs were removed by the treatment processes.

6. Applications: clinical and biological materials

6.1 Metallomics

Albarede *et al.*[115] reviewed *clinical applications of isotopic fractionation*, a topic that is not often investigated as high precision analysis is required which is best achieved using MC-MS analysers. These authors discussed Cu, S and Zn isotopic variations in tissue, serum and red cell samples of healthy volunteers and cancer patients. The ^{65}Cu : ^{63}Cu ratio in the serum of patients with colon, breast, and liver cancer was low compared to healthy subjects. The time over which Cu isotopes may change with disease progression (a few weeks) was consistent with the turnover time of the element and albumin half-life. A parallel effect on S isotopes was detected in a few untreated patients. Unlike the serum Cu, Cu in liver tumour tissue was isotopically heavy. In contrast, Zn in breast cancer tumours was isotopically lighter than in healthy breast tissue, while the ^{66}Zn : ^{64}Zn ratio was very similar in the serum of cancer patients and in controls. Results were discussed in the context of the bioinorganic chemistry *e.g.* compounds in which a metal binds to oxygen- (sulfate, phosphate, lactate) and nitrogen-bearing moieties (histidine), which favour heavy isotopes, whereas bonds with sulfur (cysteine, methionine) favour light isotopes, but the relevance of this to their clinical results was not explored.

The metabolism of *metal-containing anticancer agents* is investigated in studies to determine modes of action, drug resistance and toxicity. Most notable is the work with Pt-agents but also other compounds, of As and Ru for example. Sodium *trans*[tetrachloridobis(1*H*-indazole)ruthenate(III)] is a new drug being trialled. Distribution and accumulation of Ru after administration of this drug to a normal mouse model was investigated by Byztek *et al.*[116] After dosing, Ru concentrations in the blood rose, with plasma levels three times greater than those of the cells. Within the plasma there was initial binding to albumin and another high molecular weight species with the albumin : Ru ratio declining as the metal entered tissues and/or was excreted. Ruthenium was detected in a wide range of tissues, especially the thymus, colon, lung, liver and kidney.

Snake venom is a topic not previously discussed in these Updates. As part of a project to identify and quantify the toxic proteins, with a view towards producing therapeutic anti-venom agents Calderón-Celis and colleagues[64] developed a protocol to separate venom from three species of snake by HPLC, with parallel ESI-QTOF-MS and ICP-QQQ-MS. It will be of interest to learn what this approach will reveal and how the results can be applied to the protection of individual who may be bitten by these reptiles.

Gomez *et al.*[117] determined the distribution of *Zn in infant milk formulas* using a combination of solubility properties, SEC and ICP-MS. The work showed that Zn is present entirely within the protein fraction. When the protein fraction was further examined, the aqueous soluble protein fraction of milk formula included 90% of the zinc but only 7% and 24% were in the same fraction from soy and lactose-free formulas, respectively.

Separation of samples by SEC indicated that, in all formulas tested, Zn is bound to compounds of around 10 kDa.

Most of the speciation work mentioned in these Updates refers to applications involving just a single element. Fang *et al.*,[118] developed a procedure to determine *four As and three Hg species in the same assay*. Reverse-phase chromatography, with ICP-MS for detection, separated As^{III}, As^{V}, MMA, DMA, iHg, EtHg and MeHg from rice. Samples (0.5 g) were extracted into 1% HNO_3 with microwave heating and diluted to a volume of 25 mL. The LODs using these solutions were 0.84–2.41 and 0.01–0.04 μg L^{-1} for As and Hg species, respectively. The concentrations in a rice flour CRM and locally purchased rice were reported.

Much of the elemental speciation work we report refers to chromatographic separation of species. *Two other approaches may also be mentioned*. Zhang *et al.*[119] used 1,2,6-hexanetriol trithioglycolate, at neutral pH, to form an As^{III} hydrophobic complex, leaving the As^{V} in the aqueous phase. Orthoganol array design was adopted to optimise the liquid–liquid extraction and the analyte enhancement factor from drinking water was 87, giving an LOD of 0.03 μg L^{-1}. Drinking water samples were also analysed by Cui *et al.*[120] The work of these authors involved speciation of Cr^{III} and Cr^{VI} with the measurements being made by ETAAS. A selective reaction between Cr^{III} and 2-thenoyltrifluoracetone forms a complex that vaporises at 400 °C, while Cr^{VI} is stable up to a temperature of 1200 °C. Measurements are made of the total Cr and the Cr^{VI} concentrations with the difference reported as the Cr^{III}. Two drinking water CRMs evidenced the accuracy of the method and concentrations in tap, bottled and well water samples were reported.

Arsenic metabolism is associated with methylation efficiency, which is known to be influenced by gender, nutrition and genetics. Löveborn *et al.*[121] elected to investigate whether there are differences in methylation efficiency between children and adults. For this study, iAs, MMA and DMA were determined by ICP-MS in urine samples from 488 nine year old children. The percentage of DMA was higher and that of iAs was lower in samples from adults with the same exposure. Erythrocyte Se concentrations were also found to be positively associated with As methylation, indicating that a number of additional factors may be relevant to the metabolism of As.

Two interesting publications report on *work involving speciation of Hg*. In recent Updates magnetic solid phase extraction procedures to pre-concentrate analytes during sample preparation have been covered. Zhu *et al.*[109] added to this experience by describing the preparation of Fe_3O_4@SiO_2@gamma-mercaptopropyltrimethoxysilane magnetic nanoparticles which were then used to extract and concentrate Hg species from samples of water and fish. Rapid separation of iHg, MeHg and PhHg by HPLC-ICP-MS was effected using a mobile phase with a greater than usual concentration of MeOH. The LODs were calculated to be 0.49 to 0.74 ng L^{-1}. Analysis of CRMs provided results to confirm the accuracy of the method. Many examples of methods to analyse blood, urine and hair samples have been published in abundance but Abad *et al.*[122] have developed a common procedure which is applicable to the simultaneous determination of iHg, MeHg and EtHg, and inorganic mercury in all three sample types. The method requires 0.15 g blood, 0.5 g urine or 0.1 g hair and the same sample preparation and GC-ICP-MS conditions were employed. Results obtained from the analysis of NIST and IAEA CRMs were in agreement with the certified values. In addition, the authors reported the Hg species concentrations for SRM 955c (caprine blood) levels 2 and 4 for the first time. However, it was shown that conditions required to obtain acceptable values for caprine and human blood are not the same.

The complex *metabolism of Se has been intensively investigated* and aspects are still unclear as new intermediates continue to be identified. Akramipour *et al.*[123] claim to have developed a new methodology to determine trace elements in biological fluids and apply this innovation to the speciation of iSe in blood samples from children. The method was described as continuous sample drop flow microextraction followed by ETAAS using an Ir-modified graphite furnace. A sample, 5 mL, was slowly passed through 32 μL CCl_4 during which hydrophobic Se^{IV}-APDC is formed. The organic phase was then taken for measurement of the Se concentration by ETAAS. The work reported by Kwak and colleagues[124] addressed urinary Se metabolites. These authors proposed that volatile Se species may account for some of the unknown compounds that can be lost during analytical procedures. In the course of this study to discover potentially volatile pheromones in golden hamster urine, dimethyl selenenylsulfide, dimethyl diselenide, dimethyl bis(thio)selenide, and dimethyl selenodisulfide were detected. Whether these species are relevant to Se metabolism in other mammals or in man, or whether they are specific to the golden hamster remains to be determined. An enrichment factor of 106 was reported with an LOD of 0.02 μg L^{-1}. The total Se concentrations were determined after reduction of Se^{VI} to Se^{IV}.

6.2 Imaging with MS and XRF spectrometry

Following in a similar trend to the previous review,[1] this past year has seen *a number of review articles published summarising key areas of elemental bio-imaging*. Pozebon *et al.*[10] provided a well-researched and comprehensive review of LA-ICP-MS, capturing articles from 2014–2016, focused on the novel developments with LA cell design, calibration strategies, isotope ratio measurements, single cell analysis, nanoparticle distribution and metal-binding protein analysis. With 142 references and a large table succinctly condensing the range and breadth of bio-imaging papers, it is a useful resource. Another significant and thorough review was presented by Lee *et al.*[12] who concentrated more specifically on the use of MS-based imaging for anticancer drug research. The tutorial article covered LA-ICP-MS, nanoSIMS, TOF-SIMS, and MALDI-MS for the investigation of platinum, ruthenium and gold-based anticancer therapeutics. Sussulini and Becker[11] provided a basic overview of recent applications of LA-ICP-MS imaging in the biomedical field covering three key topics: neurodegenerative diseases, distribution of contrast agents and metallodrugs, and metalloproteomics. In a unique approach, Hare *et al.*[125] produced an online video with step-by-step instructions for a general imaging experiment of tissues by LA-ICP-MS, including

interviews with the researchers. In the modern era, this was a distinctive effort to bring scientific publications to life. Ackerman and co-workers[126] reviewed the various analytical techniques available for understanding transition element distribution within the body as both static and labile metal pools, using iron and copper as examples. The work considered the imaging of the total metal content by LA-ICP-MS, SIMS and nanoSIMS and structural methods such as XRM, XAS and electron microscopy approaches such as energy dispersive X-ray spectroscopy (EDX) and electron energy loss spectroscopy (EELS). In order to determine the mobility of metals, fluorescent probes were also included as a mechanism to understand the 'lifecycle' within a living system. The authors ultimately deduced that a suite of techniques are still required in order to obtain a full picture in complex biological systems. Collingwood and Adams[9] evaluated, compared and discussed various X-ray methods for the imaging of brain tissues in order to elucidate the role of metals in neurodegenerative disease. The techniques included X-ray microscopy, XAS, XRD, XRF, X-ray tomography, nanobeam lines and soft X-ray imaging, covering the scale from whole brain sections to the sub-cellular level. The authors concluded that X-ray approaches can be considered the analytical "Swiss army knife" for biological imaging.

The application of *LA-ICP-MS for the analysis of breast cancer tissues* was presented by de Vega *et al.*[127] to demonstrate the distribution of Ca, Cu, Fe and Zn in the growth of tumours. Quantitation was made possible with in-house prepared matrix-matched calibration standards using bovine breast tissue spiked with the elements and internal standardisation with Au. Histological samples of breast cancer tumours were obtained and compared with non-cancerous regions. Clear differences in the elemental profiles were found as the tumour contained enhanced concentrations of Ca, Cu, Fe and Zn with a heterogeneous distribution compared with non-tumour areas. The authors concluded that this technique has the potential to assist with the understanding of the role of elements in disease progression and could potentially provide an additional clinical diagnostic tool. He *et al.*[128] applied LA-ICP-MS in the investigation of Ti mobility from dental implants. Human jaw bone ($n = 7$) from 4 patients with Ti-containing implants were compared against a control group ($n = 6$), with additional tests including total elemental content using ICP-OES, histological analysis and particle identification *via* SEM-EDX. The imaging data was only qualitative but did show that the Ti intensity decreased as the distance from implant increased. The ICP-OES data added evidence that Ti levels were elevated in the test group (1940 μg kg^{-1}) compared to the controls (634 μg kg^{-1}). The roundworm *Caenorhabditis elegans* (*C. elegans*) was the focus of a review by Aschner *et al.*[129] as the transparent nematode is considered a model organism for studying metal metabolism due to its ease of handling, quick life cycle (3 days) and comparable mammalian gene expression. The authors evaluated the state of the art analytical tools available to visualise the distribution of metals within *C. elegans* along with the ability to understand metal homoeostasis and toxicity. The advantages and drawbacks of SR-μXRF, LA-ICP-MS and *in vivo* fluorescent probes were compared, with the authors summarising that the choice of technique should be driven by the study aim as it is unlikely all three can be used in the same experiment. Additionally, it was noted that challenges still arise from different sample preparation methods and with a future view that should consider metallomics approaches to gain species information.

It is not so often that publications featuring the use of ICP-TOF-MS are included in ASU Reviews, however recent instrumental developments have highlighted *ICP-TOF-MS as an emerging technology for imaging applications*. Bussweiler and co-workers[130] described how new low-volume, fast-washout cells for LA, such as the HelEx II from Teledyne/CETAC and the Bloodhound-TwoVol2 cell from ESI, have significant advantages when coupled with an ICP-TOF-MS. The article included examples of a geological sample and a kidney tissue slice. This union demonstrated promising results with faster analysis speed, enhanced resolution and, perhaps most importantly, simultaneous and multi-element capability. Whilst mass cytometry could be considered more of an applied atomic spectroscopic technique, the use of stable metal-tagged antibodies with ICP-TOF-MS has started to gain traction and the latest development in this field has expanded to LA imaging by Chang *et al.*[131] for thin tissue sections. The advantages and applications of the new system, as well as the drawbacks, were discussed. To add to this, Straus *et al.*[132] described in more detail the analytical figures of merit for this new system, showing the potential of the new technology.

An article by Bloom *et al.*[133] provided an example of *alternative MS techniques for imaging applications*. In this work, SIMS with C_{60}^+ cluster ions was used to map both Au nanoparticles and those functionalised with pharmaceuticals in single cell systems. As verification of the SIMS results, fluorophore-functionalised Au nanoparticles were also compared for visual confirmation. These results provided confirmation of the uptake ability of functionalised Au-based nanoparticles which could be used as drug delivery systems.

A paper of note which does not fall into either the MS or X-ray categories but warrants inclusion in the Imaging section was published by Thyssen and co-workers[77] who utilised *LA-ICP-OES for the elemental mapping and distribution of Ca, K and Na in tobacco plant stems and leaf petioles*. The instrumental set up was similar to conventional LA-ICP-MS, only requiring Ar make up gas to stabilise the plasma from the LA He flow and connection *via* PTFE-coated Tygon tubing, whilst the ICP-OES was operated in axial mode for maximum sensitivity. Elemental maps were generated for the two plant tissue types with only Ca quantified using in-house prepared gelatine standards. Good correlations were observed between the Ca, K and Na maps and the structural components, as identified by microscopy. However, whilst a comparison with LA-SF-ICP-MS was performed, only Ca was considered and interference from $^{40}Ar^4He^+$ hampered the detection capability of $^{44}Ca^+$ plus a lack of peak drift correction, due to the cold plasma conditions of the SF-ICP-MS, led to a qualitative assessment only. Unfortunately this left the paper lacking in terms of critical appraisal of both techniques.

The use of X-ray techniques for imaging applications is usually a significant part of this section of the ASU Review.

However, over the past year, a more limited number of examples were found. In a study by Wrobel *et al.*,[134] a combined approach utilising *μXRF and TXRF to overcome a common issue with elemental quantification in tissue samples* was proposed. The authors presented a calculation scheme to negate the effect of variations in sample density and thickness. External standard μXRF imaging, internal standard TXRF analysis and Compton intensities, enabled determination of the elemental mass fractions in kidney, liver and spleen, taking into account density and tissue thickness. Bonnemaison *et al.*[135] published a paper focused on the quantification of Ca, Cu and Zn within anterior pituitary secretory granules to understand their role in the essential process of enzymatic peptide amidation. Samples of rat pituitaries were simply frozen at −80 °C and sliced with a cryostat at 10 μm thickness, followed by XRF analysis across different sections of the gland. With additional data from the ICP-MS analysis of sub-cellular fractions (obtained from sequential centrifugation), the combination of results provided an insight into the transportation and localisation of Ca, Cu and Zn within the cell structures. Penen *et al.*[136] also described imaging on a sub-cellular level by employing high contrast TEM, TEM-EDX and nanoSIMS techniques to investigate the unicellular algae *Chlamydomonas reinhardtii*. The TEM-EDX analysis enabled detection of Ca, Fe, K, Mg, P and Zn in sub-cellular granules but the probe size (1 μm) was a limiting factor in the resolution. However, recent developments with nanoSIMS, utilising a RF plasma oxygen primary ion source, have improved the sensitivity and stability leading to a lateral resolution below 50 nm. This permitted mapping of cell organelles such as vacuoles, granules and small vesicles (approximately 200 nm in size). The high contrast TEM images achieved a superior resolution of 1 nm which confirmed the cell structures identified from the elemental mapping. The work demonstrated the capability of nanoSIMS to identify the distribution of key elements at the sub-cellular level.

6.3 Multi-element applications

6.3.1 Specimens analysed to investigate metallic implants and biomaterials. Following a number of years of prolific reported work relating to *metal-on-metal hip prostheses*, fewer publications were seen during the last year. A new observation, with potentially important implications, was presented by Simoes *et al.*[137] Metal ion levels were measured in fluids extracted from hip implant patients and *in vitro* samples of milled CoCrMo powders in solutions representative of environments in the body. Sample preparation involved using nanoporous ultrafilters which allowed complete separation of particles from free ions and complexes in solution. The analyses showed greater release of Mo ions relative to those of Co and Cr and that the Mo dissolution was enhanced by the presence of BSA. The authors suggested that the approach taken and results obtained may enable understanding of the biotribocorrosion and inflammation associated with metal-on-metal (MoM) hip implants. Analysis of Ti in blood, serum and synovial fluid using ICP-OES,[75] was mentioned in Section 4.3. Procedures to accurately determine low concentrations of Co and Cr in the same sample types have been established for some time. Nevertheless, Georgi *et al.*[138] elected to carry out an extensive validation of an ICP-MS method that would be appropriate to measure these elements in blood. Parameters evaluated included the dilution factor used during sample preparation, sample rinse time, diluent composition, and reaction cell gas flow rate. The LODs for Cr and Co in blood were determined to be 0.41 and 0.06 μg L^{-1}, respectively.

Compared to hip prostheses, greater interest is now seen in *dental implants* as questions are now being asked about the possible consequences of implants, which are usually prepared from titanium with traces of other metals. He and colleagues[128] analysed jawbones from cadavers. Slices through the jawbone (approximately 500 μm) taken 1 mm apart were prepared and analysed for 11 elements by ICP-OES and LA-ICP-MS. Except for Ti, no differences were seen between the concentrations of any elements in bone from subjects with implants, compared to the controls. Levels of Ti were greatest in the slices adjacent to an implant, which reduced as the distance increased. Particulate materials with sizes of 0.5–40 μm were found in jawbone marrow tissues at distances of 60–700 μm from the implant. In the work reported by Grenon *et al.*[139] diffusion of Ti in titanium-implanted shinbones of adult rats was shown using spatially resolved XRF spectrometry. Consistent with the observations of He *et al.*,[128] concentration decreased with distance from the implant. Dental peri-implantitis is analogous to the reactions seen in some patients with metal-on-metal hip prostheses. Similarly, the role of metals in the aetiology is unclear. Fretwurst *et al.*[140] used SR-XRF spectrometry and polarised light microscopy to examine bone and mucosal tissues taken from regions around titanium implants, in patients with signs of peri-implantitis. Nine of the 12 samples were shown to have detectable levels of Ti and Fe. Microscopy showed metal particles present in soft tissue.

In addition to hip replacements and dental implants, other metallic devices in parts of the skeleton are of interest and Gornet *et al.*[141] measured Ti concentrations in serum from patients with titanium alloy/titanium carbide composite (Ti-6Al-4 V/TiC) *cervical disc implants*. Insertion of these discs provides a treatment for degenerative cervical disc disease but wear can produce insoluble particulates and soluble metal ions. To assess the release of metal, these authors measured serum Ti concentration at intervals up to 84 months following operation, using SF-ICP-MS. Concentrations at all time points were significantly higher than preoperatively and stabilised at around 1.2 to 1.4 μg L^{-1} after about 12 months. These concentrations are much lower than in patients with other metal alloy implants.

In consideration of the concerns relating to release of metal ions from implants Matykina *et al.*[142] evaluated *in vitro* release of ions from high corrosion resistant Ti (c.p. Ti) and Ti6Al4V, with 5–10 μm-thick (PEO) coatings with graded Ca/P ratio. The samples were immersed for 1 or 8 weeks in simulated body fluid or artificial saliva, at 37 °C. Corrosive conditions were mimicked by addition of H_2O_2 and F^- was included in the artificial saliva. There was little difference in results using the different immersion solutions. The coating inhibited release of Ti from

both test materials but was more effective on the c.p.Ti. The PEO coating increased loss of Al and V compared to uncoated alloy, which was attributed to these metals being in the coating. Bearing in mind the release of metals from joint prostheses and the known cardiotoxicity associated with Co, Day *et al.*[143] developed a procedure to determine concentrations of Co, Cr and V in heart muscle by ICP-MS following closed vessel microwave digestion. Analysis of CRMs verified the accuracy of the procedure. The analytical range for all three elements was 0.5–100 ng g^{-1}. Reference intervals (mean $\pm$ sd, ng g^{-1}) were established from the results of 80 heart tissue samples and were 0.1039 $\pm$ 0.1305 Co, 0.1523 $\pm$ 0.2157 Cr and 0.0094 $\pm$ 0.0211 V. In a study to determine concentrations of Cr, Cu, Fe and Ni in saliva of subjects with fixed orthodontic appliances, Lages *et al.*[144] collected samples from patients with metal or aesthetic appliances and subjects without orthodontic treatment (30 in each group). Measurements were made by TXRF spectrometry. No significant differences among the groups were found.

6.3.2 Biological fluids and tissues. Measurements of trace element concentrations in CSF are not regularly undertaken although work from one laboratory has been noted in recent editions of these Updates. To add to relevant information Korvela *et al.*[145] measured 10 elements in CSF collected from patients with chronic neuropathic pain. The subjects were from two groups, those treated with spinal cord stimulation (which can successfully treat neuropathic pain) and those who were untreated. Analysis was performed using ICP-MS and ICP-AES. Results were compared with a CSF pool from pain-free subjects. The spinal cord stimulation treatment did not affect concentrations in the patients but concentrations of Ca, K, Mg, Na, P, Sr and Ti were significantly higher in patients compared to the CSF-control group.

Two publications described concentrations of *trace elements in serum of women during pregnancy.* Liu *et al.*[29] reported the reference values for 14 trace elements in serum from 1400 pregnant Chinese women. Samples were collected as part of the 2010–2012 China Nutrition and Health Survey and analysed using SF-ICP-MS. Some significant differences in serum concentrations were observed between different groupings of age intervals, residences, anthropometric status, and duration of pregnancy. Serum Fe, Se and Zn concentrations significantly decreased, whereas serum Cu, Co and Sr levels increased progressively through pregnancy. Choi *et al.*[146] analysed samples from 245 Korean pregnant women and 527 control subjects. They also found that Co and Cu concentrations were increased while Se and Zn were low, compared to control values and that changes were seen through the course of pregnancy. Pregnancy and neonatal outcomes, gestational diabetes, preeclampsia, neonatal birth weight and congenital abnormalities were assessed and the prevalence of preeclampsia was significantly lower in subjects with high serum Cu concentrations. Serum Co concentrations in pregnancy, given in both studies, have not been previously reported but other results are consistent with many studies. Small differences between the two sets of results, possibly associated with timings of collection, were seen but in general there was good agreement between the two data sets.

Projects to establish *trace element concentrations in different sample types collected from general populations* continue to be presented. Samples of blood and urine were collected from almost 2000 adult subjects living in Northern France and analysed for 14 elements. This work, by Nisse *et al.*[30] was presented as the IMEPOGE Study 2008–2010. Unsurprisingly, blood concentration of Cd and Pb were higher in smokers than in non-smokers. The mean urinary concentrations of most elements found in the general population of Northern France were higher than those found in the French national survey for the same period except for urinary V. However, the mean blood Pb concentration was markedly lower than found for the French national population. Pointing out that, within the European Union, Greeks have the highest proportion of smokers, Sakellari *et al.*[147] measured concentrations of Cd and Pb in blood samples from adults living in metropolitan Athens. The results were evaluated in terms of age, sex, smoking status, alcohol drinking, educational status and nutritional habits. The 95th percentile values for all subjects for Cd and Pb were 2.3 and 88 μg L^{-1}, respectively. Multiple linear regression analysis demonstrated that the predictor variables for Cd in blood were the standardised body weight, smoking, age, alcohol consumption and intake of leafy vegetables, whereas for blood Pb concentrations they were sex and age. Paglia *et al.*[148] measured the urinary excretion of 19 toxic and essential elements during one year to assess seasonal variability in concentrations. Seven participants were recruited, and collected first morning urine samples three times in a week of each month for November, January, April and July. The same balanced diet was followed during the week of collection. Twelve of the 19 elements, both essential and non-essential, had a significant seasonal variation with concentrations that increased during the summer. The authors suggest that time of the year should be considered when interpreting results. The relationship between concentrations of nine elements in early morning urine specimens and 24 h collections[31] was included in the discussion in Section 3.1.

Reference intervals for concentrations of Co, Cr and V in normal *human heart tissue* were discussed in the Section on Metallic implants and biomaterials (6.3.1). The values established were (mean $\pm$ sd, μg g^{-1}) 0.1039 $\pm$ 0.1305 Co, 0.1523 $\pm$ 0.2157 Cr, 0.0094 $\pm$ 0.0211 V.[143]

6.4. Progress for individual elements

6.4.1 Aluminium. The hypothesis that Al is actively involved in the development of Alzheimer's disease has been around for several decades and remains controversial. Past studies have shown raised Al concentrations in brain tissue from sporadic Alzheimer's sufferers and Mirza *et al.*[149] have added to this by measuring *Al in brain tissue from 12 individuals with familial Alzheimer's disease*. Quantitative measurements were made using ETAAS and Al was visualised in the tissues with fluorescence microscopy. The values measured were significantly higher than those from previous studies of sporadic Alzheimer's and normal control brains published by the same group. These findings provide further evidence of correlation between brain Al and Alzheimer's, but until

evidence of causation is found the hypothesis will likely remain controversial.

6.4.2 Arsenic. Recent ASU reviews have included multiple reports of As speciation methods and the following three papers describe useful applications of the technology. Löveborn *et al.*[121] published an interesting article investigating *As metabolism in children and adults*. The participants comprised of 488 mother–child pairs from an area of rural Bangladesh with variable concentrations of As in drinking water. Urine and blood were collected from the mothers in early pregnancy and from the children at 9 years of age. Arsenic species (iAs^{III}, iAs^{V}, MMA and DMA) were measured in the urine using an established HPLC-HG-ICP-MS method, achieving LODs of 0.2 μg L^{-1} for iAs^{III}, MMA and DMA, and 0.5 μg L^{-1} for iAs^{V}. Factors that may influence As metabolism were also determined including erythrocyte Cu, Mn, Se and Zn (by ICP-MS), urine Se (by ICP-MS), plasma folate and vitamin B_{12} (Roche ECLIA immunoassays). Children had higher %DMA and lower % iAs in their urine than their mothers, suggesting that they methylated As more efficiently. Interestingly, methylation efficiency was negatively associated with erythrocyte Se in children, in contrast to previous data from adults. The authors discussed potential mechanisms for the interaction between As and Se, noting that this novel finding warrants further investigation.

A common approach to occupational monitoring of As is to sum the concentrations of As species in urine including iAs, MMA and DMA; however, DMA excretion is increased after consumption of certain non-toxic arsenic species found in seafoods. To avoid this problem Hata *et al.*[150] reported the measurement of *urine iAs + MMA excluding DMA for As occupational monitoring*. The two methods were compared using samples from 330 Bangladeshi villagers with oral As exposure but without seafood intake, and 172 Japanese workers with seafood intake but without As exposure. The two comparisons were used to select cut-offs for monitoring As exposure in a Japanese industrial setting.

Heitland *et al.*[151] described the unfortunate case of a 4 year old boy who was poisoned with Cr^{VI} and iAs after ingestion of wood preservative. Concentrations of As and Cr were measured by ICP-MS in urine and blood, with Cr also determined in erythrocytes as an indicator of Cr^{VI} exposure. Inorganic and organic As species were measured in urine by HPLC-ICP-MS using previously published HPLC parameters. Extremely high concentrations of these analytes were recorded in the days soon after exposure (day 3: erythrocyte Cr 4540 μg L^{-1}, blood Cr 2180 μg L^{-1}, blood As 206 μg L^{-1}; day 4: urine As^{III} 109 μg L^{-1}, urine As^{V} 115 μg L^{-1}) with further measurements taken during treatment and recovery. Thankfully the child survived but required a liver transplant, DMPS chelation therapy and erythrocyte apheresis.

6.4.3 Boron. This review period has seen increased interest in B with the following two papers focused on exposure monitoring and toxicity. Michalke[152] reported the validation of an *ICP-OES assay for urine B*, designed as a simple and low cost method of monitoring occupational B exposure. The urine was prepared with a 1/20 dilution in 5% HNO_3 and detection was made using the 249.773 nm emission line. The assay achieved a LOD of 53.4 μg L^{-1}, comfortably below the concentration range expected in unexposed individuals (1.5–3.0 mg L^{-1}). "Day-to-day" imprecision was <2% (batches performed on 10 different days) and recoveries ranged from 102% to 109%. Measurement of B in a CRM, (ERM-CD 281) achieved 99% recovery, demonstrating excellent accuracy.

Igra *et al.*[153] assessed the *effect of dietary B intake on pregnancy outcomes* in a region of Argentina with high levels of B in drinking water. Serum, whole blood and urine were collected from 194 pregnant women and B, along with As, Cs, Li, were measured in the samples using ICP-MS. Serum B concentrations above 80 μg L^{-1} were inversely associated with birth size in a multivariable regression model, with a particularly strong association seen with samples collected in the third trimester. The association remained significant after adjustment for possible confounding covariates. This suggests B may be a developmental toxicant in humans and further study in other exposed populations in warranted.

6.4.4 Cerium. The catalytic activity of CeO_2 NPs has been utilised in various consumer and industrial products and their toxicology has been a focus of multiple studies. One use of CeO_2 NPs is as a diesel fuel additive and Li *et al.*[100] investigated the *biodistribution of CeO_2NPs in conditions that mimic the inhalation of diesel emissions*. Rats were exposed to two types of CeO_2 NPs through the nose: freshly combustion generated NPs and aged NPs that had been exposed to urban air conditions and UV light. Tissue, urine and faeces samples were collected, digested in concentrated HNO_3 and Ce was measured using SF-ICP-MS with an LOD of 0.002 ng L^{-1}. The majority of recovered Ce was found in the lungs and faeces with small quantities found in the extrapulmonary organs. There was no difference in the distribution of the two types of NP. The data was applied to a physiologically based pharmacokinetic model that the authors claimed "predicted the kinetics of CeO_2 nanoparticles in various organs measured in this study and suggested most of the nanoparticles were captured by phagocyte cells".

6.4.5 Chromium. Hexavalent Cr is both a sensitiser and a carcinogen and its occupational exposure is often monitored, usually by measuring total Cr in the urine of exposed workers. This is not ideal as both toxic and non-toxic Cr species are metabolised to Cr^{III} before excretion in urine and so are indistinguishable. As inhalation is the predominant route of Cr^{VI} exposure Leese *et al.*[154] investigated the *measurement of* Cr^{VI} *and* Cr^{III} *in exhaled breath condensate (EBC)*. Samples were diluted tenfold with 0.5 mM EDTA and concentrations of Cr^{III} and Cr^{VI} were measured by LC-ICP-MS using anion exchange chromatography. Detection limits for Cr^{III} and Cr^{VI} were 0.007 μg L^{-1} and 0.002 μg L^{-1} respectively and the LOQs achieved were 0.067 μg L^{-1} and 0.008 μg L^{-1} respectively. Recoveries of Cr^{III} and Cr^{VI} spiked into EBC ranged from 95% to 105% and measurement of Cr^{VI} in a proficiency testing material yielded values within the acceptable range. To assess the feasibility of using this method for occupational monitoring, EBC samples from 22 unexposed volunteers and 58 workers exposed to Cr^{VI} were analysed. Significantly higher concentrations of Cr^{III} and Cr^{VI} were found the EBC from exposed workers compared to controls although no difference was found between pre and post shift samples

from exposed workers. The authors reported that further work will include workplace air monitoring to investigate the relationship between exposure and EBC measurements.

An incident in which a 4 year old boy was poisoned with Cr^{VI} and iAs after ingestion of wood preservative,[151] was described in Section 6.4.1 Arsenic.

6.4.6 Cobalt. Occupational exposure remains the focus of attention with a useful study of *biomonitoring Co in metal factory workers exposed to Co dust*.[155] Employees were monitored over 4 months with Co measurements in urine, plasma, whole blood and erythrocytes (erythrocyte Co concentrations were presumed by the authors to represent Co-haemoglobin adducts). Measurements were made with ICP-MS in KED mode using He as the collision gas. The geometric mean of weekly urine Co measurements correlated with blood and erythrocyte Co but the individual urine results were highly variable. In a clearance study, the reduction in Co concentration after 18 days without exposure was much smaller in erythrocytes than in whole blood, plasma or urine (15.0%, 64.0%, 75.0%, 90.4%, respectively) suggesting that Co is cleared slowly from erythrocytes. The authors concluded that monitoring should be performed with analysis of whole blood or erythrocytes rather than urine, as these values represent long-term rather than short-term exposure.

The lack of SI traceable standards and reference methods for vitamin B_{12} has been addressed by Dash *et al.*[156] who published two *novel methods for determination of cyanocobalamin*. The approaches, one based on ion chromatography and the other on ICP-AES, measured the Co and P content of cyanocobalamin, allowing traceability to Co and P primary reference materials. Both techniques generated low expanded uncertainties (0.3% to 1.0%, 95% CL) which should allow the development of traceable standards for vitamin B_{12}.

6.4.7 Copper and iron. This review period included two papers from the same research group investigating the *measurement of serum elemental isotope ratios as markers of disease*. In both studies serum samples were digested with $HNO_3 : H_2O_2$ and elements purified with ion exchange chromatography prior to determination of isotope ratios by MC-ICP-MS. The results were expressed as the degree of deviation of the isotope ratio from a standard reference material (using δ notation). The first paper examined Cu isotope ratios in serum from 32 patients with end-stage liver disease[157] and found a decreased δ^{65}Cu compared with a previously established healthy reference range (difference approximately $-0.50‰$). The relatively light Cu isotope ratio became significantly heavier three months after liver transplant, although this was still below the reference range. The authors went on to look at individual cases and claimed that "the serum Cu isotopic composition seems to predict the recurrence of HCC and/or liver failure". The second paper[158] investigated Fe isotope ratios in serum from 82 patients with and without chronic kidney disease (CKD), iron deficiency and anaemia. The Fe isotope ratios were heavier in CKD patients with disease complicated by Fe deficiency (δ^{56}Fe + 0.47‰) or Fe deficiency anaemia (δ^{56}Fe + 0.98‰) than in CKD with normal Fe. No difference was seen in the δ^{56}Fe between CKD and CKD complicated with erythropoietin-related anaemia, leading the authors to conclude that δ^{56}Fe could be used to distinguish Fe deficiency anaemia and erythropoietin-related anaemia in CKD patients. Multiple regression analysis found that 70.1% of the variation in δ^{56}Fe was explained by variation in three existing serum parameters (transferrin saturation, ferritin and soluble transferrin receptors). Although the results presented in these two papers are very interesting, it seems unlikely that pathology laboratories can make use of this technology on a routine basis at present so it would need to offer. Considerable advantages over existing diagnostic tests, which are cheap, rapid, robust and well characterised are required as MC-ICP-MS is an expensive and labour intensive technique. As yet, there is not enough evidence to suggest that the measurement of isotope ratios provides diagnostic or prognostic information that is not already being captured with routine laboratory tests. We look forward to reviewing future studies that assess whether the addition of isotope ratio measurements to the existing test repertoire would improve diagnostic accuracy in real-life patient groups.

6.4.8 Gadolinium. The current review period saw the continued publication of studies focused on the measurement of Gd in a clinical context. This follows numerous reports that Gd deposits in the brain, bone and skin of patients who receive certain Gd-based MRI contrast agents. Murata *et al.*[159] evaluated these studies, which included MRI imaging of Gd *in vivo* and ICP-MS measurements of Gd in postmortem tissue. The review compared the different formulation of contrast agent, their pharmacokinetics and how their structure influenced their relative toxicity.

Mostafaei and Neie[160] reported the development of a *K-XRF method for non-invasive in vivo measurements of Gd in bone*, extending work reviewed in our previous Updates. The method used X-rays produced with a 5 GBq ^{109}Cd source, which had increased activity compared to the source in the previous study (0.17 GBq). Bone phantoms spiked with Gd were used to simulate human bone, and were able to achieve an LOD of 0.8 μg g^{-1}. A layer of plastic (lucite) was added to simulate the soft tissue covering the bone, yielding LODs ranging from 1.81 μg g^{-1} (0.61 mm lucite) to 3.47 μg g^{-1} (6.13 mm lucite). The authors stated that future studies will use human volunteers who have been exposed to Gd-based contrast agents.

Murata *et al.*[161] *measured Gd in brain, bone and skin autopsy specimens from 9 patients who had received Gd-based contrast agents*. The majority of existing evidence for contrast agent toxicity comes from "group 1 linear agents" so this study selected patients who had only received a single non-group 1 (macrocyclic or linear protein interacting) agent. The samples were digested in HNO_3 with microwave assistance and Gd was measured by ICP-MS in no-gas mode with Ir as the internal standard. Gd was found in brain tissue from all but one of the exposed patients but was below or at the LOD in control brain samples. The concentrations were significantly correlated ($r = 0.81$, p-value 0.022) with brain levels but were on average 23 times higher, leading the authors to suggest that bone Gd may be a useful surrogate for brain Gd deposition.

The review period included two *pharmacokinetic studies of Gd-based contrast agents* in rats. Smith *et al.*[162] assessed the

clearance of Gd from the brains of healthy rats after repeated intravenous dosing gadodiamide, a group 1 linear agent. Blood and tissue samples collected at 1 and 20 weeks post exposure, which were digested using HNO_3 : H_2O_2 with microwave assistance and Gd was measured using ICP-MS. After 20 weeks, Gd was below the LOD in blood but remained elevated in brain samples, although there was no histological evidence of neurotoxicity. Jost *et al.*[163] used ICP-MS and imaging with MRI to study the distribution of 7 different Gd-based contrast agents in rats. Four and a half hours after a single intravenous dose the Gd concentrations were higher in the CSF than in the blood but within 24 h, this was reversed. It suggested that Gd was rapidly cleared from the CSF although there was evidence of higher concentrations persisting in brain tissue samples. Interestingly, there were virtually no differences in the distribution of the different agents, indicating that their entry into the CSF was unaffected by their chemical structure.

6.4.9 Gold. Studies of AuNPs have featured heavily in recent ASU reviews, partly due to their ability to target drugs to certain organs and tissues. A study by Muoth *et al.*[102] assessed the *ability of different AuNPs to specifically penetrate the placenta* using a cultured 3D microtissue model. The microtissues comprised a core of fibroblasts covered with a layer of trophoblastic cells that mimic the blood-placenta barrier. These were incubated with different surface-modified AuNPs and the distribution of Au in the microtissues was studied with LA-ICP-MS. Quantitative measurements of Au were also obtained using ICP-MS after digestion with HNO_3 and HCl. The results showed improved penetration of smaller rather than larger (3–4 nm *vs.* 13–14 nm) NPs and carboxylate-modified rather than PEGylated NPs.

In similar work Mahmoud *et al.*[105] investigated the *targeting of AuNPs to different layers and structures in human skin*. The skin was donated by a patient undergoing abdominal plastic surgery and was incubated with Au nanorods that differed in their surface functional groups (neutral, anionic, cationic and hydrophobic). The stratum corneum, hair follicles and deep skin layers were separated and digested in *aqua regia* before Au was quantitated using ICP-OES. Hydrophobic polystyrene-AuNPs preferentially accumulated in the hair follicles while hydrophilic PEG-AuNPs accumulated in all skin compartments. The charged NPs did not accumulate in any of the skin regions. The distribution of the hydrophilic PEG-AuNPs was also imaged with LA-ICP-MS, confirming the distribution seen with quantitative measurements. Both studies demonstrate an interesting application of quantitative ICP-MS and imaging with LA-ICP-MS, highlighting the growing use of atomic spectroscopy in nanoparticle research.

6.4.10 Lead. The measurement of Pb in teeth has been of interest recently as it allows the assessment of Pb exposure many years after cessation of contact with the Pb source. Wang *et al.*[164] add to the existing literature with an *SR-XRF study of Pb distribution in human teeth.* Lead was found to accumulate in the secondary dentine and exterior enamel of an incisor and in the pulp and enamel of two molars; however, the low number of samples (2 molars from one subject and an incisor from a different subject) and the lack of Pb exposure history make it difficult to draw meaningful conclusions from this work.

6.4.11 Mercury. Studies investigating the association of Hg exposure with blood pressure have given inconsistent results, probably due to differences in the source of Hg encountered in different populations. In this review period Wells *et al.*[165] studied the *association of blood Hg with blood pressure* in 263 pregnant women in the USA. In contrast to previous work, Hg species (MeHg, EtHg and iHg) were measured in addition to total Hg, using a previously published method. Additionally, plasma Se and n-3 fatty acids were determined and continuous blood pressure measurements were taken during labour and delivery. The blood Hg results were grouped into tertiles in a multivariate regression model with significant associations ($P < 0.05$) found between MeHg and systolic blood pressure (one tertile increase in MeHg associated with 2.83 mmHg increase), MeHg and pulse pressure (one tertile increase in methyl Hg associated with 2.99 mmHg increase) and inorganic Hg and pulse pressure (one tertile increase in iHg associated with 2.51 mmHg decrease).

6.4.12 Osmium. Organo-metallic compounds are common candidates in the hunt for new cancer chemotherapies with Ru and Pt-containing drugs featuring in recent ASU reviews. Sanchez-Cano *et al.*[97] studied the *subcellular distribution of an organo-osmium drug candidate using SR-XRF* at the European Synchrotron (ESRF) installation in Grenoble. A beam size of 27 $\times$ 37 nm^2 was used to image Ca, Os, P and Zn in drug treated A2780 human ovarian carcinoma cells. This gave sufficient resolution to study subcellular organelles, and Os was found in the cytoplasm in small organelle-like structures, thought to be mitochondria. The results suggested that the drug has a different mode of action to existing organo-metal chemotherapy agents like cisplatin, which bind DNA and localise to the nucleus.

6.4.13 Platinum. Carboplatin is one of the most commonly prescribed chemotherapy agents and the following two reports use the Pt atom in carboplatin to make useful measurements of the drug and its adducts. Downing *et al.*[166] described the novel development of an *ICP-MS assay for determination of carboplatin in plasma filtrate* for use in therapeutic drug monitoring. Plasma filtrate Pt measurements are known to correlate with carboplatin AUC (area under the concentration/time curve) but this is the first description of an ICP-MS method. Three different centrifugal ultrafiltration devices were evaluated before the assay was validated with the chosen device. Useful data on the stability of carboplatin in blood samples was also presented.

In the second paper regarding carboplatin, Cuello-Nuñez *et al.*[167] described the *development of an SI-traceable assay for Pt-DNA adducts* intended to provide reference values for clinical research and trials. The approach measured Pt-GG (bisadduct of *cis*-diammineplatinum(II) with 2′-deoxyguanylyl-2′-deoxyguanosine) with a complex double IDA strategy using enriched ^{196}Pt and ^{194}Pt-GG with analysis by HPLC-SF-ICP-MS. The procedure was applied to carboplatin treated human lung carcinoma cells and could detect 5.54 ng Pt per mg DNA, with a measurement uncertainty ($k = 2$) of approximately 20%.

6.4.14 Plutonium. Whilst the average clinical or occupational monitoring laboratory is unlikely to need a method for Pu measurement, the same will not be true in the nuclear industry. This is the target audience for the report by Gallardo *et al.*,[39] detailing a *sensitive method for monitoring exposure to ^{242}Pu using ICP-MS in urine*. Samples underwent microwave assisted digestion with HNO_3 and extraction with an actinide binding resin (Eichrom TRU resin) prior to ICP-MS analysis. This procedure gave a minimum detectable amount (MDA_{95}) for ^{242}Pu of 0.7 pg L^{-1}, a 30 fold improvement over simple dilute and shoot ICP-MS methods.

6.4.15 Tellurium. Tellurium is a metalloid that has rarely featured in this review as it is nonessential for plants and animals and only mildly toxic; however, the widespread industrial use of Te means the consequences of exposure should be considered. Ogra[168] reviewed the use of *speciation to investigate Te biology and toxicology*, including LC-ICP-MS and LC-MS-MS studies of Te metabolites. Although progress has been made the authors note that "there are still many unknown tellurometabolites in animals and plants".

6.4.16 Titanium. The measurement of Ti was a continued focus of study during the review period, largely due to the use of Ti in surgical implants and the ubiquity of TiO_2NPs in consumer and industrial products. Golasik *et al.*[169] *reviewed toxicological studies of Ti relevant to surgical implants*, including investigations of pure metallic titanium, titanium alloys and ionic titanium. The authors noted that soluble ionic Ti (as Ti^{4+}) is the predominant species mobilised by the biodegradation of titanium alloys, and this was the focus for much of the article. Studies using cultured cells, animals and patients with dental or orthopaedic implants were summarised in a thorough and useful assessment of the literature.

Harrington *et al.*[75] described the development of an *ICP-OES method for Ti measurement in clinical specimens*. Whole blood, serum and hip aspirated fluid samples were diluted 1 : 5 with 0.5% (v/v) HNO_3 before measurement of Ti using the emission line at 336.1 nm. The intermediate imprecision of the assay was 8.6% in whole blood and 10.9% in serum but a low bias (3.3% serum, −1.0% whole blood) was seen when compared to SF-ICP-MS. The LOD of 0.6 μg L^{-1} and LOQ of 1.9 μg L^{-1} were sufficiently low for measurement of Ti in patients with a total hip replacement, but patients with hip resurfacing generally gave results below the LOQ. The measurement of Ti in a cohort of hip replacement patients provided useful information about the distribution of values, although the clinical significance of the results was not discussed.

Gornet *et al.*[141] *measured Ti in serum from 30 patients with cervical disk spinal implants* made from a titanium alloy/titanium carbide composite (Ti-6Al-4 V/TiC). The measurements were made with SF-ICP-MS (LOD of 0.2 ng mL^{-1}), with samples taken before surgery and up to 7 years postoperatively. The median Ti concentration was significantly higher than baseline at all time points, and did not change significantly between the first postoperative measurement (3 months) and the end of follow-up. The authors noted that the concentrations (range, 1.15–1.46 ng mL^{-1}) were lower than those described in studies of spine, knee and hip Ti-implants.

Two studies investigated the *toxicokinetics of TiO_2NPs after inhalation* using rats in conditions designed to simulate occupational exposure. Gate *et al.*[98] exposed young and old rats to TiO_2NP aerosols (10 mg m^{-3}) for 6 hours per day, 5 days per week and for 4 weeks. Measurement of Ti in tissues by ICP-MS at 0, 3, 28, 90 and 180 days post exposure was performed. High concentrations were seen in the lungs that cleared slowly over time. Small amounts of Ti were found in the liver and spleen but none in the blood, brain or kidneys. Pujalte *et al.*[99] exposed rats to TiO_2NP aerosols (15 mg m^{-3}) for 6 hours and sacrificed the animals at various timepoints up to 14 days. Tissues, urine and faeces were analysed with Ti measured by ICP-MS. Large quantities were found in the lungs and faeces. There was some evidence of translocation of Ti to the blood and liver although the lack of statistical hypothesis testing made the results hard to interpret. The authors also noted that "a slight increase in TiO_2 levels in olfactory bulbs and brain was visually apparent", but whether these findings were statistically significant remains an open question.

7 Applications: drugs and pharmaceuticals, traditional medicines and supplements

Recent emphasis on the measurement *of trace element concentrations in pharmaceuticals* has stimulated analytical approaches that are rapid, simple and reliable. Barrera *et al.*[170] showed that a solid sampling procedure, using HR-CS-ETAAS, could determine concentrations of Cr which were in good agreement with those obtained after total digestion in a closed-vessel microwave oven. The method had an LOD of 2.9 μg kg^{-1} and analysis of 18 drugs and three excipients had concentrations of between 0.05 and 1.92 mg kg^{-1}.

Two laboratories in the USA agreed to work together to develop a database to record the concentrations *of I in foods and dietary supplements*. Prior to this agreement the FDA had, for many years, measured I in foods as part of an annual Total Diet Study while the Nutrient Data Laboratory (NDL) of the USDA Agricultural Research Service analysed foods but did not give results for I concentrations. For the new harmonised initiative, the NDL arranged for a commercial laboratory to establish an ICP-MS method and analyse a series of foods and supplements which were also analysed by the FDA laboratory using a colorimetric method. Results from both procedures were comparable. Henceforth, values from the two organisations will be published in a database for I content of foods and in the Dietary Supplement Ingredient Database of the National Institute for Health Office of Dietary Supplements.[171]

Another publication from the US FDA reported work to assess *Se in dietary supplements*.[172] In view of the health effects of different Se species, analysis by LC-ICP-MS after heated water extraction was used to measure concentrations of seleno-amino acids, Se^{IV} and Se^{VI}, in non-selenised yeast supplements, and iSe in selenised yeast. Authors from the same laboratory also

presented a simpler, faster screening method.[91] Using EDXRF spectrometry, total Se was determined in dietary supplements with an LOD of 4 μg g^{-1}. The seleno-amino acids were also measured directly by organic MS combined with an ambient ionisation source (direct analysis in real time high resolution accurate mass–mass spectrometry; DART-HRAM-MS). Of concern to consumers and the health authorities, discrepancies between labelled ingredients and detected species were found.

Herbal medicines are widely used throughout the world. Milk thistle (*Silybum marianum*), is said to be used in the treatment of liver diseases of toxic and viral origin and also in Wilson's disease to prevent chronic liver impairment. Suspecting that medicines derived from milk thistle have high concentrations of Cu, Jedlinszki and colleagues[173] analysed ground plant material, crude milk thistle extract and products containing purified silymarin, using ICP-MS. The levels found ranged from 0.01 to 114.18 μg g^{-1} with the highest concentrations in preparations containing ground milk thistle fruits or the crude extract. Given that Wilson's disease is a condition of Cu toxicity, the authors suggested that use of these milk thistle products should be avoided for these patients. The work of Santos *et al.*,[76] using ETV-ICP-OES to measure concentrations of eight elements in powdered medicinal herbs was described in Section 4.3.

8 Applications: foods and beverages

8.1 Progress for individual elements

8.1.1 Arsenic. *Five new arsenolipids* were identified by Pereira *et al.*[63] through extraction from the bentonite clay used to clean up commercial raw fish oils. The adsorbed As species (129 μg g^{-1} bentonite) were extracted by stirring with hexane then MeOH–$CHCl_3$ (1 : 2) before fractionation on a silica gel preparative column with stepwise increases in polarity. Fractions were subjected to RP-HPLC with simultaneous detection by ICP-MS (with O_2 reaction gas) and ESI-MS (positive mode) in which two unknown arseno-hydrocarbons and five arseno-fatty acids (AsFA) were identified from the most polar elution conditions. All AsFAs showed a characteristic terminal dimethylarsinoyl moiety with linear chains conferring molecular formulae (measured $\{M + H\}^+$ m/z; mass deviation, Δm): $C_9H_{19}AsO_3$ (251.0623; $\Delta m = -0.2$ ppm); $C_{11}H_{24}AsO_3$ (279.0932; $\Delta m = -0.4$ ppm); $C_{12}H_{26}AsO_3$ (293.1087; $\Delta m = -1.7$ ppm); $C_{13}H_{28}AsO_3$ (307.1244; $\Delta m = -1.3$ ppm); $C_{14}H_{30}AsO_3$ (321.1396; $\Delta m = -2.8$ ppm). The authors state that the identification of such medium chain AsFAs awakens new interest in the presence of As-containing triglycerides or As-containing phosphatidylcholine species in marine fish oil and provided an interesting speculation about the biosynthesis of As-containing lipids, especially due to their ease of hydrolysis.

Several new approaches to the *extraction and speciation of As in food samples* were reported in the last year. The replacement of HNO_3 for As extraction using sub-critical H_2O–H_2O_2 was demonstrated by Maher *et al.*[174] to completely separate As from a wide variety of rice samples and CRMs. This was carried out in PFA vessels with microwave heating to 200 °C and 25 bar pressure. These conditions converted As^{III} to As^V which facilitated quantification by HPLC-ICP-MS because the peak retention time shifted past the void and DMA peak (Supelcosil LC-SCX cation exchange column; 250 × 4.6 mm, 5 μm). This method obviated the need for a DRC for total As determination as extracted C did not enhance ICP-MS signals. A non-chromatographic method for As speciation using electrolysis-HG, with a Cys-modified graphite electrode (GE) – previously shown to be capable of converting MeHg to Hg^0 – was described as more sensitive than conventional HG by Yang *et al.*[88] The modification of the polished and cleaned GE was carried out by initial immersion in H_2SO_4 (0.1 mol L^{-1}) to create carboxylic acid surface groups using a 1.8 V potential followed by immersion in a solution of either GSH or cysteine for the formation of peptide bonds. With a current of 0.4 A, only As^{III} is selectively reduced to AsH_3 for detection by AFS on the GSH/GE which also enables determination of total As following prior reduction. Using the CYS/GE both As^{III} and As^V are reduced at 0.6 A to give iAs while DMA is also detected at a higher current of 2.0 A; MMA was determined by difference. Calibration graphs were linear in the range 0.5–50 μg L^{-1} with RSDs ($n = 6$) which increased from 3.4% for As^{III} (20 μg L^{-1}) to 7.3% for DMA (20 μg L^{-1}). The LODs were <0.25 μg L^{-1} for all species except DMA at 0.37 μg L^{-1}.

8.1.2 Mercury. Work describing advances in *sample preparation and speciation of Hg* are included in previous Sections (3.2.2, 6.1). Further publications of interest are discussed in the section on fish and seafood.

8.1.3 Other elements. *Other elements attracting growing interest include Cr and I.* Hernandez *et al.*[175] developed a sensitive and specific procedure for determination of Cr^{VI} in cereal and dairy products by HPLC-ICP-MS. Dry samples (0.3 g) were extracted with ultrasonication (30 min) using NH_4OH (6 mL). Chromium concentration ranged from 21.6 mmol L^{-1} for bread to 54.1 mmol L^{-1} for semi-skimmed cow's milk. Online separation was carried out using an IonPac CG5A column at ambient temperature with a HNO_3–H_2O gradient prior to detection by ICP-MS. The LOQs for Cr in dairy and cereal products were 0.029 and 0.041 μg L^{-1} which represented improvement factors of 4 to 38 over previous methods. A number of cereal and dairy products were analysed and even with the low LOQs, Cr^{VI} was not detected in some. A widely-used method for total organic I, which involved adsorption onto activated carbon prior to its pyrolysis and trapping in water, was improved by Sayess *et al.*[176] and replaced the usual detection techniques with ICP-MS. Samples were adjusted to pH <1 and loaded onto minicolumns with granular activated carbon; pyrolysis gases were trapped in TMAH (2% v/v); offline determination of I by ICP-MS was further improved by using TMAH (0.1% v/v) as wash solution. Alkaline ashing with KOH and extraction into H_2O was used by Miyake *et al.*[177] to overcome low recovery due to the presence of lipophilic I in fish with standard techniques. Using ICP-MS detection, their single-laboratory validation showed recoveries ranging from 85 to 96%, short and intermediate-term RSDs were 7.7% (at 0.2 mg kg^{-1}) and there were no significant differences to RM certified concentrations.

Table 2 Food and beverages

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
Ag	Chicken (muscle, organs)	AAS; ICP-MS; SEM-EDX	An *in vivo* investigation of the distribution of AgNPs in hens following oral administration. After identification of target organs by AAS, single particle ICP-MS and SEM-EDX were applied to livers and yolks to confirm the presence of AgNPs	51
As	Cereals	XRF; ETAAS	Matrix-matched calibration standards were prepared by incubating 10 g of white rice grains with 100 mL MeOH containing DMA^V in the range 2–100 μg As. After drying at 150 °C, 5.0 g of each calibration standard were sealed into polyethylene cups. The calibration curve was linear over the concentration range 0.21–5.00 mg kg^{-1} As ($r = 0.999$). The LOD was 0.080 mg kg^{-1}. The results obtained on samples of grain cereals (6) and flour (2) agreed with those obtained by ETAAS after acid decomposition	23
As	CRM	INAA; LC-ICP-MS	An As-specific mass balance method was established and applied to the certification of an AsB standard solution CRM, metrologically traceable to the IS. This can be used for calibration in quantitative analysis of AsB, *e.g.* in fish products	20
As	CRM (apple juice)	ID-ICP-MS	An apple juice CRM was developed and certified for total As, As species (iAs and DMA), Cd and Pb	21
As	Food RMs	FI-HG-AAS	0.5–1.0 g samples were digested with conc. HCl, followed by 2 mL HBr and 1 mL of hydrazine sulphate. iAs species were extracted in $CHCl_3$ and back-extracted into 10 mL HCl 1 mol L^{-1}, prior to analysis by FI-HG-AAS. The LOQ was 0.010 mg kg^{-1}. In a collaborative method study, in the concentration range 0.074–7.55 mg kg^{-1}, repeatability (RSDr%) and reproducibility (RSD_R%) values ranged from 4.1% to 10.3% and from 6.1 to 22.8%, respectively	22
As	Cucumber (*Cucumis sativus* L. cv Joker)	XANES	As^{III} and As^V were detected in cucumber samples cooled using a liquid N_2 flow to maintain species integrity	92
As	Diet	HPLC-ICP-MS	The dietary exposure of the Italian population to iAs was investigated in the national Total Diet Study (2012–2014)	197
As	Drinking water	ETAAS	Using DLLME, the As^{III} complex formed with 1,2,6-hexanetriol trithioglycolate at neutral pH was separated from As^V. Total As (following the reduction of As^V to As^{III} by L-cysteine) and As^{III} were determined by ETAAS and As^V by difference. With an enhancement factor of 87, the LOD (As^{III}) was 0.03 μg L^{-1}, linearity was up to 3.0 μg L^{-1} and RSD% was 5.9%. Recovery from fortified samples ranged from 92.0% to 113.3%	119
As	Food and water, CRMs	HG-AAS	Using pressure-induced ionic liquid-based DLLME, the DDC–As complex formed at pH 4 was extracted into 1-hexyl-3-methylimidazolium bis(trifluoromethylsul-fonyl)-imide as the ionic liquid. With an enhancement factor of 87.5, an LOD of 0.016 μg L^{-1}, LOQ of 0.055 μg L^{-1}, linearity range up to 1.25 μg L^{-1} and RSD% of 4.89% were reported	43
As	Fruit juices (apple and orange)	ICP-QQQ-MS	As was determined in fruit juices, after microwave-assisted acid digestion in closed vessels with 2 mol L^{-1} HNO_3–H_2O_2, by means of ICP-QQQ-MS. To overcome the spectral interference of $^{40}Ar^{35}Cl^+$, determinations were carried out at mass 91 ($^{75}As^{16}O^+$) after cell reaction with O_2. The LOD was 0.013 μg L^{-1} and recovery ranged from 88% to 109%	61
As	Marine fish oil	HPLC-ICP-MS; ESI-MS	Five new arsenolipids were identified in raw marine fish oil, mainly from Peruvian anchoveta (*Engraulis ringens*), using RP-HPLC-ICP-MS and ESI-MS	63
As	Rice	HPLC-ICP-MS	4 As species (As^{III}, As^V, MMA^{III} and DMA^V) and 3 Hg (Hg^{II}, MeHg and EtHg) were determined simultaneously, within a 20 min run, by ion-pairing RP-HPLC-ICP-MS	118
As	Rice	ICP-MS; HPLC-ICP-MS	The concentration of total As was determined by ICP-MS and 5 As species (As^{III}, As^V, MMA^{III} and DMA^V) by HPLC-ICP-MS, using extraction with 5 mmol L^{-1} malonic acid and an isocratic mobile phase	198
As	Rice, canned tuna, water, CRMs	ETAAS	A novel sorbent, based on a magnetic nanoparticle composite, was synthesised and applied to the speciation of As^{III} and As^V	110

Table 2 (*Contd.*)

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
As	Rice, RMs	HPLC-ICP-MS; ICP-MS; ETAAS	Extraction of iAs from rice samples (0.2 g dry mass) was achieved in a microwave oven with 9 + 1 mL of H_2O—30% v/v H_2O_2 at 200 °C and 25 Bar. It gave comparable results to extraction with 2% v/v HNO_3 ($y = 1.046 + 0.010$, $r^2 = 0.997$, $p < 0.0001$), but with simplified chromatograms	174
As	Rice, water, SRM	HG-AFS	Sulfydryl-containing substances (L-cysteine and glutathione) were applied to modify the performance of the graphite electrode used for electrolytic HG-AFS. The modifier and applied current allowed the selective and quantitative conversion of As^{III} or As^{III} + As^{V} to AsH_3, in the presence of MMA and DMA, as well as the determination of total As and DMA. In aqueous solutions, LODs (3 s) for As^{III}, iAs and total As were 0.25 μg L^{-1}, 0.22 μg L^{-1} and 0.10 μg L^{-1}, respectively	88
As	Rice, wine	ICP-QQQ-MS	As^{III} was oxidised to As^{V} with H_2O_2 during sample preparation, followed by separation of the sum of iAs (as As^{V}) from other As species using a short, narrow bore, 5 μm chromatographic column. Determinations were carried out by ICP-QQQ-MS using O_2 as the reaction gas	62
As	Seafood	AFS	5 As species (AB, As^{III}, As^{V}, DMA and MMA, extracted from seafood samples using 2% HCOOH and ultrasonication, were separated in <8 min on a Hamilton PRP-X100 anion-exchange column using gradient elution with 33 mmol L^{-1} CH_3COONH_4 and 15 mmol L^{-1} Na_2CO_3—10 mL EtOH at pH 8.4. Recoveries from spiked samples ranged from 72.6% and 109% and RSD% was <3.6%	199
As	Seafood (fish, mussels, shrimps, edible algae), rice-based products (Jasmine and Arborio rice, spaghetti, flour, crackers), CRMs	HPLC-ICP-MS	After extraction with a 1 + 4 MeOH–H_2O solution, the separation of As^{III}, As^{V}, MMA^{III} and DMA^{V} was achieved in 7 min using an anion-exchange narrow-bore Nucleosil 100 SB column and 12 mmol L^{-1} $NH_4H_2PO_3$ (pH 5.2) as the mobile phase, at a flow rate of 0.3 mL min^{-1}. Instrumental LODs were in the range 0.3–0.4 ng As mL^{-1} and RSD% was <3%	200
As	Seaweed (red laver, green laver, sea tangle, sea mustard, and hizikia), seafood (snow crab, red snow crab, octopus, octopus minor, and squid)	IC-ICP-AES	Seaweed and seafood samples were dried and ground to fine powder prior to extraction and determination of total As and As species (As^{III}, As^{V}, AsB, DMA, MMA) by IC coupled with end-on-ICP-AES. Recoveries ranged from 98.2 to 99.1%	201
As	Seaweeds (Dulse, Nori, Kombu, Wakame, Sea Spaghetti, canned seaweed), CRM	HPLC-ICP-MS	Water soluble As species were extracted from edible seaweeds within 7 min using pressurised hot water. The LOQs were in the range of 47 to 101 ng g^{-1} and repeatability RSDs% were <18%	202
Ca	Powdered milk, solid dietary supplements	LIBS; ICP-AES	The results of the direct determination of Ca, K, and Mg by LIBS, using two calibration strategies, were compared with ICP-AES after acid digestion	80
Cd	CRM (apple juice)	ID-ICP-MS	See As, ref. 21	21
Cd	Food (bread, rice and fruit juice) SRM (rice flour)	FAAS	Rice (1 g), fruit juice (200 ml) and bread (5 g) samples were digested by wet oxidation with conc. HNO_3—conc. $HClO_4$—30% H_2O_2. The residues were re-dissolved in 2 mL of 0.5 M HNO_3, then made up to 50 mL with triple distilled water. After pre-concentration on a newly synthesised chelating resin, Cd and Zn were determined by FAAS with LODs and LOQs of 1.5 and 5.1 μg L^{-1} (Cd) and 1.2 and 4.1 μg L^{-1} (Zn), respectively. The resin's capacity was determined as 53.96 mg g^{-1} (Cd) and 24.19 mg g^{-1} (Zn) at pH 8.0. The analysis of a SRM gave results in agreement with the certified values and recovery from spiked samples ranged from 96.1% to 100.3% (Cd) and from 97.67% to 105.7% (Zn)	203
Cd	Food and water CRMs	GD-AES	A method based on atmospheric pressure GD-AES with a miniaturised liquid drop anode was developed and applied to the direct determination of Cd in 50 μL samples. The LOD ranged between 0.20 and 0.40 μg L^{-1}, linearity was up to 1000 μg L^{-1} and RSD% was between 2 and 5%. Recovery for CRM values and spiked water samples ranged from 95.2% and 99.6%	71

Table 2 (*Contd.*)

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
Cd	Herbs	ETAAS	Pre-concentration of Cd from herb samples was achieved using solidified floating organic drop micro-extraction with 1-(2-pyridylazo)-2-naphthol (PAN) as the chelating agent, with an RSD% ($n = 6$) of 2.67% at 1.0 μg L^{-1}. Recovery ranged from 94.5% to 110.2%	46
Cd	Soft drinks	ETAAS	The extraction and pre-concentration of sub-ppt levels of Cd and Pb from soft drinks was achieved by DLLME, with 500 μL of $(CH_3)_2CO$ (Cd) or 700 μL of CH_3CN (Pb) as dispersive solvents, 60 μL of CCl_4 as extraction solvent for both analytes and 500 μL of complexing agent (1.5% DDTC). Recovery ranged from 91% to 113% for Cd and from 95% to 108% for Pb. RSD% were <10% (Cd) and <7% (Pb). LODs were 0.006 and 0.072 ng L^{-1} for Cd and Pb, respectively	204
Ce	Drinking water, surface water	ICP-MS	ZnO and CeO_2NPs were detected in surface and drinking water using spICP-MS, with a dwell time of 0.1 ms or lower. Conventional drinking water treatments were found to be effective in removing most (from 60% to >95%) of these NPs	53
Ce	Edible plants (cucumber, tomato, soybean, and pumpkin)	ICP-MS	The size and size distribution of CeO_2NPs, as well as the concentration of Ce and CeO_2NPs, were determined simultaneously, using spICP-MS, after enzymatic digestion of plant shoots with macerozyme R-10	205
Cl	Milk, CRM (waste water)	HR-CS-ETAAS	Cl was determined indirectly by measuring the molecular absorption of SrCl at 635.862 nm, with a Zr-coated GF and 25 μg Sr, with an LOD of 1.76 μg mL^{-1}. Pyrolysis and molecule-forming temperatures were 600 °C and 2300 °C, respectively	206
Co	Vitamin B_{12}	ICP-AES	The metrological traceable quantitation of cyanocobalamin (vitamin B_{12}) was achieved *via* measurements of Co and P, carried out by ICP-AES and IC. The expanded uncertainty (95% CL) ranged from 0.3 to 1%	156
Cr	Cereal products, dairy products	IC-ICP-MS	3 mL milk or 0.3 g of solid samples were extracted with NH_4OH in an ultrasonic bath. After centrifugation and filtration of the supernatant, samples were analysed by IC-HPLC-ICP-MS, using IonPac CG5A and IonPac CS5A columns. Gradient elution was achieved using 2 mmol L^{-1} HNO_3 and ultrapure water as the mobile phase. The LOQs ranged from 0.6 μg kg^{-1} (dairy products) to 0.8 μg kg^{-1} (cereal products). The relative bias observed on spiked samples ranged from −3% to 14% over the concentration range 1–90 μg kg^{-1}. Cr^{VI} was not detected, even in the presence of measurable total Cr values	175
Cr	Drinking water, SRMs	ETAAS; IC-ICP-MS	By adding *in situ* 2-thenoyltrifluoracetone, the Cr^{III} complex vaporised at 400 °C, whereas Cr^{VI} was released at 1200 °C, during ETAAS. Cr^{III} concentration was obtained as the difference between total Cr and Cr^{VI} concentrations in the sample. LODs were 0.046 μg L^{-1} (Cr^{VI}) and 0.039 μg L^{-1} (total Cr), with RSDs% ($n = 5$) of 3.1% (1.0 μg L^{-1} Cr^{VI}) and 2.8% (1.0 μg L^{-1} Cr). A comparison was carried out with IC-ICP-MS	120
Cr	Milk and baby foods, SRM	ETAAS	Slurries were prepared by 10 min sonication with ultrapure water, whereas liquid samples were only diluted, prior to analysis by ETAAS, with 500 μg Rh as the permanent modifier. An LOD of 1.43 μg L^{-1} was achieved, linearity was up to 50.0 μg L^{-1} and RSD% ($n = 8$) ranged from 1.5% to 11.8%	207
Cu	Beef	LIBS; ETAAS	Cu measurements by LIBS, coupled with modelling techniques, were assessed, in combination with ETAAS determinations as a reference, as a tool to detect offal adulteration in beef	78
Cu	Distilled alcoholic beverages (palinka)	HR-CS-ETAAS; XRF	After direct injection, followed by a fast heating program, Cu was determined with an LOD of 0.03 mg L^{-1}. The linearity was up to 10–15 mg L^{-1} and average recovery was 100.9 ± 8.5%. A comparison with TXRF was carried out	66

Table 2 (*Contd.*)

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
Cu	Food samples (wheat flour, corn flour, rice flour and tahini), SRMs	FAAS	For the determination of Cu, Fe and Zn in food samples by FAAS, microwave-aided digestion with a HNO_3–H_2O_2 mixture provided the best results over other sample preparation methods, including wet digestion and other reagents (HCl, HNO_3). Analysis of CRMs gave results with percent relative errors from −2.5% to +3.0%. LODs and LOQs were 14.5 and 48.3 μg $L^{-1}$for Cu, 16.4 and 54.6 μg L^{-1} for Fe, and 10.8 and 36.0 μg L^{-1} for Zn	208
Cu	Infant formula (rice, oats, bovine milk and soybean based)	HR-CS-ETAAS	After direct solid sampling, pyrolysis, 1300 °C, was applied for both analytes, whereas atomisation was carried out at 2300 °C and 2100 °C for Cu and Mn, respectively. For Cu (sample mass 3.0 mg), LOD and LOQ were 0.003 μg g^{-1} and 0.01 μg g^{-1}, respectively, whereas, for Mn (sample mass 1 mg) LOD and LOQ were 0.01 μg g^{-1} and 0.04 μg g^{-1}. Analysis of a CRM (rice flour) showed no significant differences between measured and certified values	67
Eu (as label)	Seafood	CE-ICP-MS	Diethylenetriamine-*N*,*N*,*N*′,*N*″, *N*″-pentaacetic acid was coupled with saxitonin, a paralysing shellfish toxin, while simultaneously forming a complex with Eu^{3+}, to provide a label for the indirect detection of saxitonin in seafood. An absolute LOD of only 0.38 fmol (using 100 nL sample injection) and an RSD% ($n = 5$) <7% were achieved	58
F	Food CRMs (14), branded tea samples (13)	ICP-QQQ-MS	A mass shift strategy was applied to the determination of F in food and tea samples by ICP-QQQ-MS. F was converted to BaF^+ and selectively extracted into the reaction cell with other species at m/z 157, then reacted with 10% NH_3—90% He (8.0 mL min^{-1}), and determined at m/z 208	60
Fe	Chicken	LIBS; LIF	LIBS and LIF measurements were applied to detect spoilage in chicken meat over 3 days after slaughter, using Fe and Mg as markers	79
Fe	Food samples (wheat flour, corn flour, rice flour and tahini), SRMs	FAAS	See Cu, ref. 208	208
Fe (histamine)	Fish, dairy products, alcoholic beverages	FAAS	Histamine was determined indirectly by FAAS, with an LOD of 0.25 μg L^{-1}. Sample preparation consisted of formation of a complex of histamine with Fe^{III} (25 mmol L^{-1}) and 2′,4′,5′,7′-tetrabromofluorescein (eosin, 5 mmol L^{-1}) at pH 4.5, followed by extraction, using ultrasonic assisted CPE, into the micellar phase of polyethyleneglycoldodecylether (Brij 35, 10 mmol L^{-1})	70
Hg	Environmental water, wastewater, tap water, fish, CRM (DORM-2)	HPLC-ICP-MS	A novel procedure for the speciation of Hg^{2+}, $MeHg^+$ and $PhHg^+$ was developed using SPE with Fe_3O_4@SiO_2@gamma-mercaptopropyltrimethoxysilane magnetic NPs. Species separation was achieved in 8 min. LODs for Hg^{2+}, $MeHg^+$ and $PhHg^+$ were in the range of 0.49–0.74 ng L^{-1}. Intra- and inter-day RSDs% ($n = 5$) were <9.0% and 12%, respectively	109
Hg	Fish (common carp: muscle, gill, intestine, liver, gallbladder, brain, eye), CRMs	CV-AFS	Hg species in 1 mg sample were extracted into 100 μL eluent by MWCNT assisted matrix solid-phase dispersion and transported to AFS after single-drop solution electrode GD-induced CV generation	35
Hg	Rice	HPLC-ICP-MS	See As, ref. 118	118
Hg	Seafood (muscle, liver, gonads and eggs), CRMs (hair, cod fish tissue, swordfish tissue)	CV-AAS	Samples (0.6–1.5 g) were digested with 1 mL 0.1% L-cysteine—1 mL 5 M NaOH at 80 °C for 1–2 h, then made up to 5 mL with distilled water. After extraction of fat with 6 mL IBMK and washing of the remaining solution with C_6H_{14}, determination of total Hg was carried out, whereas, for the measurement of MeHg concentrations, further extraction into 6 mL $C_6H_5CH_3$ was necessary using 2 mL of the aqueous extract, 2 mL of 5 M HBr and 0.5 mL of 2 M $CuCl_2$. The organic layer was then back-extracted into a 0.2% L-cysteine—2% $NaCH_3COO^-$ solution and analysed. Analysis of CRMs, recovery tests and a comparison with GC-ECD (MeHg) confirmed the reliability of the procedure	87

Table 2 (*Contd.*)

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
Hg	Seafood, CRMs (12)	VG-CCP-AES	Samples were subjected to a treatment with 47% HBr, followed by extraction of $MeHg^+$ in $C_6H_5CH_3$ and back-extraction in 1% L-cysteine. Hg determination was achieved, after FI UV photo-reduction of $MeHg^+$ in 0.6 mol L^{-1} HCOOH, by VG-CCP-AES. The LOD and LOQ were 2 μg kg^{-1} and 6 μg kg^{-1}, respectively, and recovery was 99 ± 8%	74
I	Drinking water	ICP-MS	The content of total organic I in water was determined by ICP-MS after adsorption of the sample (pH < 1) on granular activated carbon, combustion, and trapping of the combustion products using a 2% (v/v) TMAH solution. In between samples, washing of the ICP-MS with 0.1% (v/v) TMAH was necessary to remove any carry-over	176
I	Fish, CRM	ICP-MS	A novel sample preparation, consisting of ashing fish samples with KOH and extracting I in water from the ash, was evaluated. The LOQ was 0.20 mg kg^{-1}, repeatability and intermediate precision RSDs% were 7.7% and recovery ranged from 85 ± 9% to 96 ± 7%	177
I	Food and dietary supplements	ICP-MS Colorimetry	As part of the process to build a national database of I content in food and food supplements, two US bodies established the comparability of results obtained by either ICP-MS or a standard colorimetric method, thus allowing the pooling of data obtained independently by the two organisations	171
K	Powdered milk, solid dietary supplements	LIBS; ICP-AES	See Ca, ref. 80	80
Lanthanides	Milk	ICP-MS	The distribution of lanthanides was identified as a fingerprint for traceability purposes in the milk production chain	181
Mg	Chicken	LIBS; LIF	See Fe, ref. 79	79
Mg	Powdered milk, solid dietary supplements	LIBS; ICP-AES	See Ca, ref. 80	80
Mn	Fish muscle, oyster, bovine liver, CRMs	HR-CS ETAAS	Three elements (Mn, Ni and Rb) were determined in food samples by solid sampling and HR-CS-ETAAS. LODs were 0.005 μg g^{-1} (Mn), 0.002 μg g^{-1} (Ni) and 0.1 μg g^{-1} f(Rb)	68
Mn	Infant formula (rice, oats, bovine milk and soybean based)	HR-CS-ETAAS	See Cu, ref. 67	67
Ni	Fish muscle, oyster, bovine liver, CRMs	HR-CS ETAAS	See Mn, ref. 68	68
Pb	CRM (apple juice)	ID-ICP-MS	See As, ref. 21	21
Pb	Food (grains, vegetables, seafood), CRMs	ETV-AFS; ICP-MS	The concentration of Pb in mg food samples was determined in less than 6 min, by solid sampling and ETV-AFS. The LOD was 3.0 pg and LOQ was 10.0 pg. The RSD% observed on CRMs was <5.0% and recovery ranged from 90.0% to 110.0%. A comparison with microwave-aided digestion and ICP-MS showed no significant difference	90
Pb	Game meat	ICP-MS	spICP-MS was applied to detect PbNPs (40 to 750 nm) in game meat, from animals shot with Pb-containing bullets	54
Pb	Soft drinks	ETAAS	See Cd, ref. 204	204
Rb	Fish muscle, oyster, bovine liver, CRMs	HR-CS ETAAS	See Mn, ref. 68	68
REEs	Plant samples, CRM	ICP-MS	Dry-ashing was considered adequate for plant sample digestion, in comparison with dry-ashing with a HF step or wet digestion with H_2O_2–HNO_3. LODs between 0.02 ng L^{-1} (Lu) and 13 ng L^{-1} (La) were achieved. RSD% ranged from 1% to 4%	34
REEs (10)	Indian basmati rice, soil, water	ICP-QMS; MC-ICP-MS	The concentrations of ten REEs (Ce, Dy, Er, Eu, Gd, La, Nd, Pr, Sm, Yb) were determined by Q-ICP-MS in Indian basmati rice and local soil samples, as potential markers of geographical authenticity. In addition, the ^{87}Sr : ^{86}Sr isotopic ratio was studied by MC-ICP-MS, in the same samples and in samples of the water used for irrigation, after extraction on a Sr-specific resin. The ^{87}Sr : ^{86}Sr isotopic ratio could discriminate between Indian Basmati rice and other rice samples, except Australian and Thailand rice	180

Table 2 (*Contd.*)

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
S	Edible salts	LIBS; LA-ICP-AES; LA-ICP-MS; ICP-AES	Different analytical techniques were compared for the determination of S in edible salts from different geographical origins. LIBS and LA-ICP-AES showed the best accuracy and LIBS could identify S chemical forms (S^{2-} or SO_4^{2-}) associated with origin and quality of edible salt	209
Se	Dietary supplements	XRF	XRF was applied for the rapid screening of total Se for label verification, whereas the selenoamino acid fraction was quantified using HR-MS/MS. This approach required <40 min per sample	91
Se	Fish tissue (muscle, liver), CRMs	HPLC-ICP-MS	Several sample preparation methods were evaluated, using CRMs, for the determination of SeCys and/or SeMet in marine fish tissues. After enzymatic hydrolysis, SeMet was measured by anion or cation exchange chromatography coupled with ICP-MS. After a complexation step for SeCys, followed by enzymatic hydrolysis and SEC, SeCys and SeMet were determined by means of C_8 ion-pair RP-HPLC-ICP-MS. Recoveries for spiked samples were 84% ± 9% (SeCys) and 97% ± 9% (SeMet), respectively	40
Se	Food samples (including cereals, edible seaweeds, mushrooms, soya and tea leaf), CRMs	HG-AFS	0.5–1 g of finely ground food samples were acid digested with 15 mL of 3 + 1 HNO_3–$HClO_4$, on a hot plate, followed by addition of 5 mL of 6 mol L^{-1} HCl to reduce Se^{VI} to Se^{IV}, and dilution to 50 mL. A double CPE was performed, first, using 5% (m/v) Triton X-114—1 g L^{-1} APDC, to extract the Se^{IV}-APDC complex into the surfactant rich phase, then adding a mixture of 16% (v/v) HCl—20% (v/v) H_2O_2 to convert Se^{IV}-APDC into free Se^{IV} and back extract it into the aqueous phase. Recovery ranged from 95.6% to 105.2%	210
Se	Vegetables (garlic, onion, leek, broccoli and cauliflower)	ETAAS	After extraction of Se^{IV} and Se^{VI} from freeze-dried and powdered samples with 0.1 mol L^{-1} HCl, one portion of the extract was treated with 37% HCl to reduce Se^{VI} to Se^{IV} prior to analysis. Another portion of the extract was further pre-concentrated by LLME of the Se^{IV}-APDC complex with 50% (w/v) trihexyl(tetradecyl)phosphonium decanoate in $CHCl_3$ as the ionic liquid. Recovery from samples spiked with either Se^{IV} or Se^{VI} ranged from 94% to 102%	44
Sn	Edible vegetable oil	HPLC-ICP-MS	4 organotin compounds were determined simultaneously in edible vegetable oil samples, after freezing with MeOH and purification by matrix solid-phase dispersion with graphitised carbon black. LODs and LOQs ranged from 0.28 to 0.59 μg L^{-1} and from 0.93 to 1.8 μg L^{-1}, respectively	49
Sr	Indian Basmati rice, soil, water	ICP-QMS; MC-ICP-MS	See REEs, ref. 180	180
Tl	Water, spinach, CRMs	ETAAS	Tl pre-concentration was achieved with DLLME, by forming a complex of Tl^{3+} with Br^- and cetylpyridinium chloride, followed by extraction into a mixture of 1.5 mL MeOH—150 μL $CHCl_3$. The LOD was 0.03 μg L^{-1}, linearity was up to 2 μg L^{-1} ($r = 0.9983$) and RSD% at 1 μg L^{-1} Tl^{III} was 4.1% ($n = 6$)	45
Zn	CRMs	MC-ICP-MS	6 biological CRMs (fish muscle, bovine muscle, pig kidney, human hair, human blood serum and human urine) with certified Zn concentrations were characterised for their ^{66}Zn : ^{64}Zn isotope ratio	25
Zn	Drinking and surface water	ICP-MS	See Ce, ref. 53	53
Zn	Food (bread, rice and fruit juice) SRM (rice flour)	FAAS	See Cd, ref. 203	203
Zn	Food samples (wheat flour, corn flour, rice flour and tahini), CRMs	FAAS	See Cu, ref. 208	208
Zn	Infant formula	SEC-ICP-MS	SEC-ICP-MS was applied to investigate the availability of Zn from infant formula and the results compared with those obtained by *in vitro* methods (solubility and dialysability)	117
Various	Red wine samples	LIBS	The combined application of LIBS and neural networks to 38 red wine samples allowed classification of them according to protected designation of origin. A new sample pre-treatment with a dry collagen gel avoided working with liquid samples	81

Table 2 (*Contd.*)

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
Various	Vegetables (*Daucus carota, Spinacia oleracea, Cynara scolymus, Raphanus staivus, Coriandrum sativum*)	EDXRF; XRF	EDXRF and μXRF were applied to investigate the presence and distribution of major and trace elements in edible vegetables from soils irrigated with municipal treated wastewater	211
Various (4)	Single rice seed	ICP-MS	The simultaneous determination of As, Cd, Cr and Pb in single rice grains was achieved using matrix solid phase dispersion, with MWCNT as the dispersing agent, and ICP-MS detection. Comparison with microwave-aided digestion (n = 30) did not show significant differences. LODs were 5.0 ng g^{-1} (As), 0.6 ng g^{-1} (Cd), 10 ng g^{-1} (Cr) and 2.1 ng g^{-1} (Pb), respectively. RSDs% (n = 6) were <7.7%	47
Various (5)	Canned vegetables	Various	The outcome of a proficiency test (IMEP-118) for the determination of total As, iAs, Cd, Hg, Pb and Sn mass fractions in peas in brine was reported, addressing critical issues related to harmonised compliance assessment for such samples	28
Various (5)	Tap water, mineral water, Yellow River water and waste water	GD-AES	A liquid cathode GD-AE spectrometer was constructed and applied to the simultaneous determination of Ca, K, Mg, Na and Zn. The LOD for Ca was 0.19 mg L^{-1} whereas lower values (from 0.02 to 0.05 mg L^{-1}) were obtained for K, Na, Mg and Zn	72
Various (6)	Insects (grasshopper, cricket, buffalo worms, mealworms), Sirloin beef	ICP-AES	The availability of Fe and other elements (Ca, Cu, Mg, Mn and Zn) from 4 commonly eaten insect species were compared to that from Sirloin beef using *in vitro* methods and ICP-AES	179
Various (6)	Milk, SRM	FAAS; SEM	Cd, Cu, Cr^{III}, Mn, Ni and Pb were quantitatively sorbed on *Aspergillus niger* loaded on TiO_2NPs at pH 6.0 and flow rate of 3.0 mL min^{-1}. Elution was obtained with 2.0 mL of 0.5 mol L^{-1} HNO_3, with a pre-concentration factor of 600. LODs (3 s) ranged from 0.08 μg L^{-1} (Mn) to 0.61 μg L^{-1} (Pb) and RSDs were <3%	111
Various (7)	Drinking water	XRF	The on-site determination of Cd, Cu, Fe, Hg, Mn, Pb and Zn in drinking water was achieved by filtering a 50 mL sample, adjusted to pH 5 with acetate buffer, through an iminodiacetate chelating disk, which was then coated with adhesive cellophane tape, dried at 100 °C for 60 s and examined by XRF. The LODs were 7.6 μg L^{-1} (Cd), 4.0 μg L^{-1} (Cu), 9.4 μg L^{-1} (Fe), 4.4 μg L^{-1} (Hg), 6.6 μg L^{-1} (Mn), 3.2 μg L^{-1} (Pb) and 3.6 μg L^{-1} (Zn). Recoveries from spiked samples ranged from 89.0% to 110%	212
Various (10)	Ethiopian green coffee (*Coffea arabica* L.)	ICP-AES	The content of Ba, Ca, Cu, Fe, K, Mg, Mn, P, S and Si was determined in 49 coffee bean samples, representing varieties from different Ethiopian regions. Statistical analysis of the results (PCA and linear discriminant analysis) provided models for origin traceability	182
Various (12)	Edible vegetables, CRMs	XRF; ICP-MS	A sample preparation procedure for TXRF, consisting of suspension of 20 mg of powdered sample in 1 mL deionised water containing 10 μg Ga as internal standard, followed by 5 min sonication in an ultrasonic bath, was proposed and compared with microwave-aided acid digestion and acid digestion in a tube block heater. No statistically significant differences were observed	213
Various (13)	Bee pollen	ICP-AES	13 elements (Ba, Ca, Cd, Cr, Cu, Fe, Li, Mn, Mo, P, Pb, V and Zn) were determined in 5 bee pollen samples, dried at 42 °C for 20 h. Prior to analysis, samples were treated with 20% HNO_3 for 24 h, to exclude any contaminated material, then wet acid digested with a 65% HNO_3–H_2O_2 mixture at 150 °C for 5 days and the digests made up to 10 mL with deionised H_2O	214
Various (13)	Juice and milk	ICP-AES	The performance of a high-pressure microwave-assisted flow digestion system was evaluated. Juice samples were digested with 3.7 mol L^{-1} HNO_3—0.3 mol L^{-1} HCl, whereas for partially skimmed and whole milk only conc. HNO_3 was used. No significant differences were observed with the results from other conventional, batch digestion systems	41

Table 2 (*Contd.*)

Element	Matrix	Technique(s)	Sample preparation/comments	Ref.
Various (20)	Chitosan (food grade)	ICP-MS	Chitosan was dissolved in 3% citric acid—HCl for the determination of 20 trace elements by DRC-ICP-MS using Bi, In, Sc and Y as internal standards and matrix matching for calibration. Instrumental LODs ranged from 0.6 to 19.0 ng L^{-1}. Recovery from spiked samples varied from 89.50% to 109.00% and RSD% from 1.17% to 4.05%	215
Various (23)	Dietary supplements	ICP-MS	The content of 23 elements in 67 food supplements based on algae, garlic, yeast, fish and krill oils was determined and the maximum daily intake calculated. No risk to healthy adults was revealed	216

8.2 Single and multielement applications in food and beverages

8.2.1 Human milk and infant formula. The availability of Zn in infant formula was studied by Gomez *et al.*[117] through acid digestion/dialysis, a three-step simulated gastrointestinal digestion and SEC-ICP-MS. The proportion of Zn in the protein fraction, separated using Tris–HCl (100 mM, pH 6.8, was dependent on the milk source: milk-based products contained 90% whereas soy and lactose-free products were very low at 7–24%. Solubility of Zn in cow's milk by *in vitro* methods was 60–70% with soy milk being lower at 23%. *In vitro* dialysable Zn concentrations yielded lower than expected results (Zn < 11%) as SEC-ICP-MS showed that Zn was associated with low *Mr* compounds (0.1–7 kDa) that were small enough for intestinal absorption, suggesting dialysis data should be interpreted with caution. Vacchina *et al.*[178] determined the total Hg and MeHg content in a large number of human milk samples using a proprietary advanced Hg analyser, AMA (following optimisation and validation) and ID-ICP-MS, respectively. The AMA was loaded with a solid, dried sample which was then thermally decomposed, with O_2 carrier gas sweeping gaseous products into an isothermal catalytic furnace. The resultant Hg^0 vapour was trapped in an Au amalgam and analysed using AAS. The technique yielded an LOQ of 0.22 μg kg^{-1} dw, short- and intermediate-term RSDs of 2–11% and 4–12%, respectively and trueness bias of −0.1-9%. A comparison of MeHg determination was made between GC-MS and HPLC-ID-ICP-MS with the latter technique retained for use in the subsequent study. Samples were pre-concentrated by freeze drying prior to analysis. The LOQ was 0.16 μg kg^{-1} dw and intermediate RSDs were 4–8%. Analysis of human milk samples from 180 subjects yielded a range of total Hg from LOD to 142 μg kg^{-1} dw and MeHg from LOD to 3.67 μg kg^{-1} dw.

8.2.2 Vegetables, vegetable oils, fruits and nuts. With the aim of determining As toxicity to cucumber plants in the presence of different soil Fe species, Gerenyi *et al.*[92] developed a new *in vivo* XANES method with use of liquid N_2 vapour cooling. Model plants (*Cucumis sativa* L Joker) were hydroponically grown with either $FeCl_3$ or Fe^{II}-ascorbate. After 5 d growth, plants were then exposed to As^V in concentrations of 20, 40, 60, 80, 100 μM for 24–48 h. The hypocotyl was separated for mounting and cryogenically cooled to 77 K before analysis: this not only protected the plant material from damage by the X-ray beam but also preserved the oxidation status of the As species. The presence of Fe-ascorbate was shown to have negated the detrimental effect of As toxicity.

8.2.3 Fish and seafood. Yoshimoto *et al.*[87] reported a simplified *methodology for determining Hg and MeHg in seafood* by using IBMK to de-fat samples, in place of $CHCl_3$. The aqueous phase was then used for total Hg determination whilst MeHg was extracted using HBr, toluene and $CuCl_2$ with back extraction in L-cysteine and sodium acetate for quantitative determination using CVAAS. Recovery was demonstrated as >95% using CRMs, although other figures of merit were not given. The authors analysed the muscle, liver, gonad and squid nidamental glands for total Hg and MeHg from numerous commercially-available fish, squid and sea urchin products in Kagoshima, Japan. This work demonstrated correlations of MeHg concentrations between muscle and testes/ovaries/nidamental glands across the species studied.

8.2.4 Meat and meat products. *Spoilage in meat* is difficult to assess without destructive testing, prompting an investigation of LIBS and LIF for this purpose.[79] Chicken breast samples were analysed on three consecutive days post slaughter. The cyanise and carbon molecular bands were taken as indicators of protein content, subsequently validated using a conventional protein analyser. The ratio of ionic to atomic spectral lines Mg^{II} : Mg^{I} and Fe^{II} : Fe^{I} was also shown to be a marker of meat tenderness. In the LIF spectra, an additional line (696.08 nm) to that of tryptophan (492 nm) was shown to correlate with the proliferation of *Pseudomonas aeruginosa* ($R^2 = 0.96$). Casado-Gavalda *et al.*[78] also used LIBS, to detect offal adulteration in minced beef. A calibration model was created and validated using PLS-regression from Cu concentrations determined by ETAAS, with a cross validation correlation of 0.85. Beef liver presented a mean Cu concentration of 98 ppm while heart and kidney levels were lower at 4.0 ppm and 4.3 ppm, although still higher than lean meat at 0.8 ppm.

Entomophagy as a sustainable source of dietary protein is witnessing a marked increase in interest. Latunde-Dada *et al.*[179] assessed the nutritional mineral composition (Ca, Cu, Fe, Mg, Mn and Zn) of four 'commonly-eaten' insects, with reference to

beef sirloin, using ICP-AES. Cricket and beef had higher Ca, Fe and Mn compared with grasshopper, meal- and buffalo worm although all insects had significantly higher Fe solubility.

8.2.5 Food and wine authenticity. *Isotope ratios of Sr* are certainly the most ubiquitously used for food authenticity. Lagan *et al.*[180] used ^{87}Sr : ^{86}Sr in combination with REEs for the geographical characterisation of Indian basmati rice ($n = 82$) samples. Strong correlations were observed between rice Sr isotope ratios and those of soil silicate SiO_4^{2-} and CO_3^{2-} fractions. Whereas this ratio can be used to differentiate samples from India from other countries, only samples from Uttar Pradesh could be distinguished from other regions of India, the difference being attributed to higher ^{87}Sr : ^{86}Sr ratios in this region. There also appeared to be variations with REEs but no serious multidimensional statistical tests were carried out to demonstrate their value. Aceto *et al.*[181] also used lanthanides to classify the geographical origin of milk. They demonstrated a continuous relationship in REEs from soil, through fodder, to milk types and creams, which would guarantee a robust traceability in the milk production chain. It was also possible to differentiate local craft dairies from local industrial and foreign producers. Sometimes the simple approach can also work in differentiating well-defined product types as demonstrated with green coffee beans from Ethiopia.[182] Just 10 elements (Ba, Ca, Cu, Fe, K, Mg, Mn, P, S and Si), determined by ICP-AES, were sufficient to discriminate three areas of East, South and West Ethiopia with a classification rate of 92% and also identify the different varieties of *Coffea arabica* (classification rate of 79%).

Conflicts of interest

There are no conflicts of interest to declare.

Abbreviations

AAS	Atomic absorption spectrometry
AB	Arsenobetaine
AC	Arsenocholine
ACN	Acetonitrile
AE	Atomic emission
AES	Atomic emission spectrometry
AFS	Atomic fluorescence spectrometry
APDC	Ammonium pyrrolidine dithiocarbamate
ASU	Atomic Spectrometry Update
CL	Confidence limits
CPE	Cloud point extraction
CRM	Certified reference material
CS	Continuum source
CSF	Cerebrospinal fluid
CV	Cold vapour
DART-HRAM-MS	Direct analysis in real time high resolution accurate mass–mass spectrometry
DDTC	Diethyldithiocarbamate
DLLME	Dispersive liquid–liquid microextraction
DMA	Dimethylarsenic
DNA	Deoxyribonucleic acid
DPhT	Diphenyl tin
DRC	Dynamic reaction cell
Dw	Dry weight
EBC	Exhaled breath condensate
EDTA	Ethylenediamine tetraacetic acid
EDXRF	Energy dispersive X-ray fluorescence
EELS	Electron energy loss spectroscopy
ERM	European RM
ESI	Electrospray ionisation
ETAAS	Electrothermal atomic absorption spectrometry
EtHg	Ethyl mercury
FAAS	Flame atomic absorption spectrometry
FAES	Flame atomic emission spectrometry
FDA	Food and Drug Administration
FI	Flow injection
Fs	Femtosecond
FT-MS	Fourier transfer MS
GD	Glow discharge
GE	Graphite electrode
GC	Gas chromatography
GSH	Glutathione
HCC	Hepatocellular carcinoma
HDPE	High density polyethylene
HG	Hydride generation
HILIC	Hydrophilic interaction liquid chromatography
HPLC	High performance liquid chromatography
HR	High resolution
IAEA	International Atomic Energy Authority
iAs	Inorganic arsenic
IBMK	Isobutyl methyl ketone
IC	Ion chromatography
ICP-AES	Inductively coupled plasma atomic emission spectrometry
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma optical emission spectrometry
ID	Isotope dilution
IEC	Ion exchange chromatography
IL	Ionic liquid
INAA	Instrumental neutron activation analysis
IP	Ionisation potential
ISE	Ion selective electrode
iSe	Inorganic selenium
JCGM	Joint Committee for Guides in Metrology
KED	Kinetic energy discrimination
LA	Laser ablation
LC	Liquid chromatography
LIBS	Laser induced breakdown spectroscopy
LIF	Laser induced fluorescence
LOD	Limit of detection
LOQ	Limit of quantification
MALDI	Matrix-assisted laser desorption ionisation
MC	Multicollector
MeHg	Methyl mercury
MMA	Monomethylarsonic acid
MRI	Magnetic resonance imaging
MS	Mass spectrometry
MSPD	Matrix solid phase dispersion
MWCNT	Multi-wall carbon nanotubes
NDL	Nutrient Data Laboratory

NIST	National Institute of Standards and Technology
NP	Nanoparticle
PE	Polyethylene
PEG	Polyethylene glycol
PEO	Plasma electrolytic oxidation
PFA	Perfluoroalkoxy alkane
PhHg	Phenyl mercury
PIGE	Particle-induced gamma ray emission
PIXE	Particle-induced X-ray emission
PT	Proficiency testing
PTFE	Poly(tetrafluoroethylene)
PVP	Polyvinylpyrrolidone
Q-ICP-MS	Quadrupole-ICP-MS
QQQ	Triple quadrupole
REE	Rare earth element
RM	Reference material
RP	Reversed phase
RSD	Relative standard deviation
SEC	Size exclusion chromatography
SeCys	Selenocysteine
SF	Sector field
SEC	Size exclusion chromatography
SEM	Scanning electron microscopy
SEM-EDX	SEM-energy dispersive X-ray spectrometry
SeMet	Selenomethioneine
SI	International System of units
SIMS	Secondary ion MS
SOD	Superoxide dismutase
SPE	Solid phase extraction
spICP-MS	Single particle ICP-MS
SRM	Standard reference material
SR-XRF	Synchrotron radiation X-ray fluorescence
TBT	Tributyl tin
TEM	Transmission electron microscopy
TIMS	Thermal ionisation MS
TMAH	Tetramethyl ammonium hydroxide
TOF	Time-of-flight
TPhT	Triphenyl tin
TXRF	Total reflexion XRF
UV	Ultra violet
XANES	X-ray absorption near-edge structure
XAS	X-ray absorption spectroscopy
XRA	X-ray absorption
XRF	X-ray fluorescence
XRM	X-ray microscopy

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