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A high-resolution ICP-MS method for the determination of 38 inorganic elements in human whole blood, urine, hair and tissues after microwave digestion

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ABSTRACT

Inductively coupled plasma-mass spectrometry (ICP-MS) is currently the reference method for the determination of inorganic elements, and has many applications in healthcare and the environmental field. The objective of the present study was to develop and validate a high-resolution ICP-MS method for the simultaneous quantification of 38 elements in samples of human whole blood, urine, hair and tissues after microwave mineralization. The samples were incubated with nitric acid, hydrogen peroxide and internal standards prior to microwave mineralization for 25 min. The analysis was performed with an Element XR ICP-MS and validated using commercial reference standards (whole blood, urine, and hair) and in-house quality control samples. The 38 elements were detected in low-, medium- or high-resolution mode, depending on interferences and sensitivity. The lower and upper limits of quantification were adjusted for each element. The method was linear for all elements (correlation coefficient > 0.996), and the inter- and intraday precision values (coefficient of variation) were below 15%. Samples from a clinical trial were used to confirm the high-resolution ICP-MS method's suitability for the assessment of patient samples.

1. Introduction

Inductively coupled plasma mass spectrometry (ICP-MS) is used widely to analyze trace and ultra-trace elements in biological matrices. Human exposure to elements released from toxics, drugs and implanted medical devices is conventionally monitored by assaying serum, blood, and urine. However, tissue or hair samples often provide additional useful information. For instance, toxic elements can enter the lungs through the inhalation of smoke or contaminated air. Furthermore, elements absorbed by the digestive and/or pulmonary tract can find their way into the bloodstream and become distributed throughout and incorporated into the body's various tissues - including the hair. Hence, measurements in hair can reflect the body's cumulative exposure to the various elements. Lastly, some elements may be deposited directly on the hair by external contamination [1–4].

The limits of detection (LOD) associated with conventional quadrupole ICP-MS mean that the technique is not ideal for the simultaneous quantification of several trace elements in human blood or serum samples [5]. Inductively coupled plasma - sector field mass spectrometry (ICP-SFMS) has greater sensitivity and resolving power; this produces LOD in the pM range [6] and enables useful performance over a broad concentration range. The use of ICP-MS to assay trace elements in human samples (with or without prior mineralization) has already been reported. For example, ICP-MS with an octopole-based collision/reaction cell has been used to quantify 37 trace elements in human blood [7]. After acid sample dilution, high-resolution ICP-MS has been applied to the determination of 20–42 elements in human urine and serum; the concentrations were similar to those observed in non-

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Table 1
Limits of quantification and characteristics of the calibration curve for each element (n = 6, values are quoted as the mean ± standard deviation).

Element	LLOQ (μM)	ULOQ (μM)	Range of the calibration curve (Log)	Number of calibration standards	Slope of the calibration curve	y-intercept of the calibration curve	Correlation coefficient for the calibration curve
Ag	0.015	10	2.8	10	0.92 ± 0.09	0.010 ± 0.015	0.9994 ± 0.0007
As	0.01	1	2.0	7	0.09 ± 0.01	− 0.0015 ± 0.0033	0.9987 ± 0.0016
Au	0.01	1	2.0	10	0.72 ± 0.05	0.0014 ± 0.0034	0.9972 ± 0.0028
Ba	0.002	5	3.4	8	0.47 ± 0.03	− 0.0032 ± 0.0103	0.9987 ± 0.0009
Be	0.01	0.5	1.7	7	0.01 ± 0.0008	− 0.000005 ± 0.00001	0.9990 ± 0.0013
Bi	0.004	1	2.4	8	4.2 ± 0.5	0.0016 ± 0.017	0.9988 ± 0.0023
Cd	0.005	10	3.3	11	0.17 ± 0.01	− 0.0036 ± 0.0026	0.9995 ± 0.0005
Ce	0.0002	1	3.7	9	3.1 ± 0.3	0.00035 ± 0.0009	0.9998 ± 0.0003
Co	0.001	20	4.3	12	3.0 ± 1.0	0.12 ± 0.11	0.9993 ± 0.0005
Cr	0.02	10	2.7	8	2.3 ± 0.8	0.025 ± 0.023	0.9999 ± 0.0002
Cs	0.002	1	2.7	8	3.16 ± 0.17	0.0052 ± 0.0081	0.9996 ± 0.0005
Cu	5	200	1.6	15	2.0 ± 0.7	0.058 ± 1.89	0.9986 ± 0.0011
Fe	1	500	2.7	15	3.1 ± 1.1	3.1 ± 2.0	0.9997 ± 0.0002
Ge	0.01	1	2.0	7	0.21 ± 0.02	− 0.0011 ± 0.0012	0.9991 ± 0.0005
Hf	0.0000001	1	7.0	15	1.0 ± 0.1	− 0.0052 ± 0.0032	0.9983 ± 0.0012
Hg	0.025	10	2.6	11	0.2 ± 0.01	0.0020 ± 0.0026	0.9996 ± 0.0003
La	0.00005	1	4.3	11	32.5 ± 3.0	− 0.0089 ± 0.0030	0.9998 ± 0.0002
Mn	0.05	2	1.6	10	3.5 ± 1.2	0.0041 ± 0.018	0.9996 ± 0.0002
Mo	0.005	1.5	2.5	11	0.24 ± 0.02	− 0.0007 ± 0.0002	0.9994 ± 0.0002
Ni	0.05	50	3.0	15	0.76 ± 0.27	0.041 ± 0.041	0.9998 ± 0.0001
Pb	0.025	5	2.3	7	3.0 ± 0.7	− 0.038 ± 0.096	0.9991 ± 0.0010
Pd	0.005	0.5	2.0	7	0.25 ± 0.04	− 0.00062 ± 0.00053	0.9963 ± 0.0029
Pt	0.001	0.1	2.0	10	0.76 ± 0.02	− 0.00006 ± 0.0002	0.9997 ± 0.0002
Rb	0.1	50	2.7	10	1.2 ± 0.1	0.85 ± 0.42	0.9996 ± 0.0018
Ru	0.000001	0.01	4.0	13	0.40 ± 0.03	0.00002 ± 0.000007	0.9994 ± 0.0010
Sb	0.00001	0.1	4.0	10	0.52 ± 0.05	− 0.0001 ± 0.0005	0.9975 ± 0.0011
Se	0.1	10	2.0	11	0.02 ± 0.003	− 0.021 ± 0.029	0.9989 ± 0.0010
Sn	0.005	1	2.3	11	0.70 ± 0.04	− 0.0019 ± 0.0005	0.9994 ± 0.0004
Sr	0.1	10	2.0	7	1.79 ± 0.11	0.012 ± 0.046	0.9997 ± 0.0002
Te	0.001	0.05	1.7	7	0.03 ± 0.003	− 0.000004 ± 0.000009	0.9991 ± 0.0008
Th	0.00025	0.01	1.6	7	3.9 ± 0.3	− 0.00004 ± 0.0001	0.9981 ± 0.0012
Ti	0.038	10	2.4	7	0.17 ± 0.003	0.0013 ± 0.0038	0.9998 ± 0.0002
Tl	0.00025	0.05	2.3	7	Quadratic regression		
U	0.000001	0.001	3.0	15	49.6 ± 3.3	− 0.00002 ± 0.00008	0.9995 ± 0.0003
V	0.02	1.5	1.9	9	2.2 ± 0.8	− 0.026 ± 0.097	0.9996 ± 0.0003
W	0.0004	1	3.4	8	1.0 ± 0.2	− 0.00007 ± 0.0019	0.9999 ± 0.0001
Zn	10	200	1.3	7	0.27 ± 0.10	0.066 ± 0.20	0.9990 ± 0.0007
Zr	0.00001	0.1	4.0	15	0.90 ± 0.06	− 0.0013 ± 0.0019	0.9968 ± 0.0019

occupationally exposed populations [6,8]. Methods for the ICP-SFMS quantification of 4–8 abundant elements in human blood and/or serum after microwave digestion have also been reported [9,10]. Microwave digestion was shown to enhance the recovery of elements and to be more reproducible and accurate than wet or dry digestion procedures [11,12]. However, all the methods reported to date have various shortcomings: (i) they can only detect a small number of elements simultaneously; (ii) for some elements, the LOD is above the concentration found in clinical samples; (iii) analyses are restricted to blood and serum samples (i.e. hair and other human tissues could not be assessed); and (iv) microwave digestion is not applied.

The objective of the present study was to develop and validate a method for the simultaneous quantitation of 38 trace elements in human tissues, urine and whole blood samples, following microwave mineralization. The method's suitability for the analysis of clinical samples was also demonstrated.

2. Materials and methods

2.1. Chemicals and reagents

Analytical and internal standards were purchased from LGC Standards (Molsheim, France). ICP-MS-grade nitric acid, hydrochloric acid, hydrogen peroxide and Triton X100 were obtained from Fisher Scientific (Illkirch, France). Whole blood, urine and hair quality control (QC) samples were supplied by Centre de Toxicologie du Québec (Québec, Canada). Ultrapure deionized water (18 mΩ) was obtained from a water station (Purelab Flex, Elga Labwater, Antony, France). Argon 5.0 was purchased from Messer (Puteaux, France).

2.2. Working and calibration standard solutions

Working and calibration standard solutions were prepared by diluting 1000 μg mL^{-1} or (for Cu, Fe, Rb, and Zn) 10000 μg mL^{-1} single-element standard solutions. Three sets of 15 calibration standards were prepared: the first set contained all the elements (except those detailed thereafter) in 5% HNO_3 in metal-free plastic tubes, the second contained Sb, Hf, Au, Pt, and Ru in 20% HCl in metal-free plastic tubes, and the third contained Hg only in borosilicate tubes. The chosen standard concentrations were based on those published previously for human samples. Hence, the calibration range differed from one element to another: Goulle et al. and Cesbron et al. reported elemental concentrations in whole blood, plasma, urine and hair samples from a population of healthy volunteers in France [3,13]; Heitland and Koster reported on the concentrations of 37 trace elements in blood samples from inhabitants of northern Germany [7]; Schultze et al. described whole blood and serum concentrations of metals in a Swedish population-based sample [14]; Alimonti et al. and Minoia et al. reported concentrations of metals in blood, serum or urine samples from healthy adults living in Rome [15] or Lombardy [16]. To prepare the calibration curve, 10 μL of each calibration standard solution were added to 190 μL of deionized water. Quality control samples were stored at −20 °C, whereas calibration standard stock and working solutions were stored at room temperature.

Table 2
Validation data for whole blood QC samples. Measured concentrations are presented for three different days as the median [range] (μM) from six replicate samples. The values of the CVs correspond to the intraday, interday and total CVs, respectively.

	Blood level 1: QM-B-Q1505			Blood level 2: QM-B-Q1506		
	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)
Ag	0.022	0.023 [0.022–0.024]	5.1	0.061	0.062 [0.057–0.065]	6.9
		0.024 [0.023–0.025]	14.9		0.063 [0.062–0.078]	7.9
		0.022 [0.019–0.023]	7.1		0.063 [0.058–0.066]	7.0
As	0.036	0.044 [0.037–0.047]	8.8	0.21	0.24 [0.20–0.29]	12.2
		0.044 [0.037–0.050]	7.4		0.23 [0.21–0.25]	7.9
		0.041 [0.038–0.042]	8.7		0.24 [0.21–0.27]	11.8
Ba	0.026	0.048 [0.046–0.049]	6.5	0.058	0.076 [0.075–0.079]	2.6
		0.042 [0.040–0.048]	13.6		0.082 [0.078–0.085]	9.4
		0.043 [0.041–0.049]	7.7		0.078 [0.077–0.080]	4.1
Be	0.30	0.45 [0.44–0.48]	4.6	1.9	2.8 [2.7–2.9]	4.2
		0.42 [0.38–0.45]	13.0		2.8 [2.6–2.8]	7.2
		0.42 [0.39–0.43]	6.3		2.7 [2.3–2.8]	4.6
Bi	0.013	0.013 [0.011–0.016]	9.3	0.034	0.035 [0.026–0.039]	14.4
		0.014 [0.014–0.015]	14.2		0.038 [0.035–0.044]	14.5
		0.013 [0.012–0.014]	10.0		0.035 [0.030–0.047]	14.4
Cd	0.053	0.061 [0.057–0.066]	5.7	0.12	0.13 [0.13–0.14]	4.8
		0.061 [0.052–0.066]	9.3		0.13 [0.12–0.14]	4.5
		0.057 [0.055–0.058]	6.3		0.13 [0.12–0.14]	4.8
Co	0.019	0.018 [0.017–0.019]	6.9	0.035	0.035 [0.033–0.037]	6.3
		0.021 [0.018–0.022]	14.6		0.032 [0.031–0.034]	11.0
		0.020 [0.017–0.022]	8.3		0.034 [0.030–0.039]	7.0
Cr	0.096	0.090 [0.066–0.102]	14.4	0.11	0.10 [0.09–0.10]	7.8
		0.094 [0.076–0.106]	12.0		0.11 [0.10–0.12]	14.2
		0.086 [0.079–0.108]	14.1		0.10 [0.10–0.12]	8.9
Cu	12.8	12.2 [11.8–12.7]	9.5	47.8	40.0 [38.2–40.9]	2.6
		13.1 [8.7–13.8]	15.0		39.3 [38.1–39.8]	2.6
		11.0 [10.8–11.3]	10.3		40.2 [38.2–41.3]	2.6
Hg	0.030	0.038 [0.036–0.041]	3.7	0.008	0.010 [0.009–0.011]	12.1
		0.036 [0.035–0.037]	9.3		0.010 [0.009–0.011]	0.9
		0.039 [0.038–0.039]	4.8		0.010 [0.008–0.012]	11.0
Mn	0.28	0.28 [0.26–0.30]	6.5	0.41	0.40 [0.38–0.43]	4.5
		0.27 [0.26–0.30]	6.0		0.39 [0.37–0.41]	6.4
		0.26 [0.25–0.31]	6.4		0.41 [0.37–0.44]	4.8
Mo	0.031	0.075 [0.056–0.086]	12.3	0.051	0.090 [0.071–0.093]	12.6
		0.076 [0.067–0.079]	14.7		0.077 [0.062–0.093]	13.8
		0.063 [0.056–0.082]	12.7		0.086 [0.065–0.089]	12.8
Ni	< LLOQ	NA	NA	0.18	0.15 [0.14–0.22]	11.9
					0.16 [0.13–0.17]	10.5
					0.17 [0.17–0.18]	11.7
Pb	1.1	1.0 [0.9–1.1]	6.3	2.4	2.1 [1.9–2.3]	4.8
		1.0 [1.0–1.0]	3.6		2.1 [2.0–2.2]	3.2
		1.0 [0.9–1.0]	6.1		2.0 [1.9–2.2]	4.6
Pt	0.0021	0.0022 [0.0019–0.0023]	9.4	0.012	0.014 [0.013–0.015]	3.6
		0.0020 [0.0019–0.0026]	12.7		0.014 [0.013–0.014]	5.2
		0.0020 [0.0018–0.0020]	9.9		0.013 [0.013–0.014]	3.9
Sb	0.029	0.033 [0.031–0.036]	9.7	0.11	0.13 [0.12–0.13]	2.0
		0.035 [0.023–0.037]	6.5		0.12 [0.12–0.13]	6.8
		0.032 [0.031–0.033]	9.3		0.13 [0.12–0.13]	3.0
Se	2.2	2.2 [2.1–2.5]	10.2	2.9	3.1 [2.7–3.5]	11.3
		2.5 [2.1–2.7]	12.5		2.7 [2.5–3.4]	13.6
		2.7 [2.2–2.8]	10.5		3.1 [2.7–3.5]	11.6
Sn	0.029	0.032 [0.027–0.037]	14.9	0.17	0.15 [0.14–0.16]	6.3
		0.032 [0.021–0.038]	6.9		0.16 [0.13–0.18]	4.5
		0.032 [0.029–0.038]	14.2		0.16 [0.15–0.17]	6.1
Sr	1.0	1.2 [1.1–1.2]	3.0	3.2	3.6 [3.4–3.8]	3.2
		1.1 [1.1–1.2]	4.1		3.5 [3.4–3.6]	5.0
		1.2 [1.1–1.2]	3.2		3.5 [3.3–3.6]	3.5
Te	0.020	0.021 [0.020–0.022]	6.4	0.062	0.064 [0.059–0.066]	3.8
		0.021 [0.020–0.022]	6.3		0.066 [0.064–0.069]	11.5
		0.019 [0.019–0.023]	6.4		0.069 [0.066–0.073]	5.3
Th	0.0029	0.0032 [0.0030–0.0035]	3.7	0.0086	0.0101 [0.0091–0.0103]	3.4
		0.0033 [0.0032–0.0033]	1.6		0.0100 [0.0098–0.0102]	2.3
		0.0033 [0.0032–0.0033]	3.5		0.0100 [0.0096–0.0102]	3.3
Tl	0.017	0.016 [0.016–0.017]	2.7	0.038	0.034 [0.031–0.036]	3.9
		0.015 [0.015–0.016]	8.3		0.036 [0.035–0.038]	7.8
		0.017 [0.016–0.017]	3.8		0.036 [0.034–0.036]	4.5
U	0.0020	0.0020 [0.0019–0.0021]	5.8	0.0035	0.0035 [0.0034–0.0039]	4.7
		0.0018 [0.0017–0.0018]	12.8		0.0038 [0.0035–0.0039]	13.9
		0.0019 [0.0018–0.0023]	7.0		0.0034 [0.0033–0.0035]	6.6

(*continued on next page*)

Table 2 (*continued*)

	Blood level 1: QM-B-Q1505			Blood level 2: QM-B-Q1506		
	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)
V	0.024	0.036 [0.030–0.040]	6.4	0.052	0.059 [0.055–0.064]	5.3
		0.038 [0.037–0.041]	10.4		0.058 [0.054–0.060]	4.9
		0.039 [0.036–0.040]	7.0		0.060 [0.055–0.064]	5.3
Zn	97	112 [106–117]	4.8	166	176 [156–182]	5.2
		113 [101–118]	11.5		178 [170–189]	7.8
		101 [99–107]	6.1		186 [165–193]	5.6

2.3. Sample preparation

Whole blood, urine and tissue samples were processed directly, whereas hair samples were washed first to eliminate any external contamination (using the method developed by the International Atomic Energy Agency, with some modifications [17–19]). The strand of hairs was washed once with 0.1% Triton X100, three times with deionized water and then once with acetone, prior to drying in an oven at 40 °C.

Next, 200 µL of urine, whole blood or plasma, 15 mg of lung tissue, or 10 mg of hair were added to quartz tubes containing 10 µL of the internal standard solution (10 µg/mL gallium and iridium, and 100 µg/mL indium and scandium). Two hundred microliters of nitric acid and 200 µL of hydrogen peroxide were then added. The tubes were capped, transferred to the microwave reaction chamber (Ultrawave, Milestone, Sorisole, Italy) and then microwaved at 1500 W (heating from ambient temperature to 220 °C over 15 min, followed maintenance at 220 °C for 10 min) at a pressure of 110 bar. After the samples had cooled, they were transferred to 15 mL polypropylene tubes and made up to a volume of 6 mL with deionized water.

2.4. Instrumentation and the analytical procedure

The samples were handled using an ASX-520 autosampler (CETAC technologies, Omaha, NE, USA), a PFA-ST microflow nebulizer, and a PC[3] Peltier-cooled cyclonic quartz chamber (both from Elemental Scientific Instruments, Ltd, Birmingham, UK) maintained at + 2 °C. A demountable quartz torch with a quartz injector (internal diameter: 1.75 mm), a platinum sampler, and skimmer cones were used (Elemental Scientific Instruments, Ltd). The ICP-MS instrument was an Element XR (Thermofisher, Les Ulis, France) controlled with Element ICP-MS software (v3.1.2.242). The operating conditions (torch position, lenses, gas flows and detector voltage) were optimized daily in low-, medium- and high-resolution modes, using a 100 ppt tuning solution (Thermofisher). This yielded oxide levels ($^{238}U^{16}O/^{238}U$) below 10%, and a resolution of around 4000 and 10000 in the medium- and high-resolution modes, respectively. Mass calibration was performed as required. The main ICP-MS detection parameters are shown in Supplementary Table 1. The parameters used to detect the elements of interest and their internal standards are summarized in Supplementary Table 2.

2.5. Validation of the ICP-MS method

The ICP-MS method was validated using reference standards (at two different concentrations) for whole blood, urine, and hair. Since theoretical concentrations were not available for all 38 elements in the matrix, a set of in-house QC samples at three concentrations (containing the elements spiked into blank water) were also analysed. To assess intra- and interday performance levels, all QC samples were analysed on three different days as six replicates. Calibration curves included a sample blank, a zero sample, and 7–15 calibration standards (depending on the element) over a preselected concentration range for each element (based on the literature data for the different matrices [3,7,13–16]). The intensity of each element in the sample blank was subtracted from the intensity measured in each sample.

For each element, the ratio between the peak area and the peak area of the corresponding internal standard was plotted against the concentration; the relationship was then probed in a regression analysis. The correlation coefficient was analysed for each calibration curve. The precision was defined as the coefficient of variation (CV), which was determined for each QC and had to be less than ± 15%. The lower limit of quantification (LLOQ) was defined as the calibration standard that gave a signal intensity of at least ten times the standard deviation recorded for sample blanks.

2.6. Analysis of clinical trial samples

To confirm its suitability for clinical samples, the method developed here was used to measure elements in whole blood, hair and lung samples from 25 patients participating in a clinical trial (designed to assess the role of trace elements in lung cancer; NCT01949181).

3. Results and discussion

3.1. Sample preparation

A variety of vessels and reagent mixtures were tested for microwave mineralization. Disposable borosilicate glassware contaminated samples with several elements, whereas quartz tubes provided reproducible results and low levels of contamination (results not shown). The composition of the mineralization mixture was also optimized by comparing 100, 200 or 400 µL HNO_3 in the presence of absence of 100 or 200 µL of H_2O_2 for the mineralization of 200 µL of sample matrix. The composition with 200 µL HNO_3 and 200 µL H_2O_2 yielded the most complete digestion (with the absence of particulate matter and a sufficient amount of sample) and so was used for the subsequent experiments. This digestion method was found to be appropriate for all samples: whole blood, urine, hair, or lung tissue. In contrast to conventional dilution methods, the microwave mineralization method destroys organic molecules in the matrix; this avoids the formation of deposits on the cones, reduces fouling of the instrument, and therefore increases the sensitivity.

3.2. ICP-MS analysis

Most elements were detected in low-resolution mode. However, polyatomic or isobaric interferences (due to the environment or the sample preparation) occurred for some other elements. Hence, Ti, V, Cr, Mn, Fe, Co, Ni, Cu, Zn and Tl had to be detected in medium-resolution mode, and Ge, As, Se and Pd had to be detected in high-resolution mode [6]. Although a higher resolution improved the method's specificity, the transmission was about 10% in medium-resolution mode and 1.5% in high-resolution; this decreased the sensitivity. However, our method was sensitive enough to detect all the elements at the required concentrations.

We also optimized the number of runs and passes, which therefore modified the sample volume and the sensitivity. With our final

Table 3
Validation data for urine QC samples. The measured concentrations are presented for the three different days as the median [range] (μM) from 6 replicate samples. The values of the CVs correspond to the intraday, interday and total CVs, respectively.

	Urine level 1: QM-U-Q1503			**Urine level 2: QM-U-Q1504**		
	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)
Ag	0.051	0.045 [0.040–0.047]	5.8	< LLOQ	NA	NA
		0.049 [0.047–0.051]	12.8			
		0.047 [0.040–0.049]	7.1			
As	1.3	1.4 [1.2–1.5]	7.7	0.67	0.77 [0.72–0.81]	9.0
		1.5 [1.4–1.5]	8.8		0.74 [0.64–0.84]	14.5
		1.4 [1.3–1.6]	7.8		0.67 [0.63–0.76]	9.9
Ba	0.031	0.047 [0.045–0.051]	6.3	0.012	0.038 [0.037–0.039]	13.8
		0.046 [0.042–0.048]	12.6		0.033 [0.029–0.039]	14.6
		0.053 [0.046–0.054]	7.4		0.031 [0.030–0.046]	13.9
Be	0.30	0.40 [0.39–0.44]	4.9	1.4	2.0 [1.8–2.0]	4.6
		0.40 [0.39–0.41]	4.5		2.0 [1.8–2.1]	9.2
		0.39 [0.37–0.44]	4.8		1.9 [1.7–2.0]	5.4
Bi	0.12	0.11 [0.10–0.13]	14.7	0.025	0.031 [0.027–0.031]	11.4
		0.12 [0.09–0.13]	11.8		0.026 [0.025–0.036]	5.7
		0.10 [0.09–0.14]	14.3		0.031 [0.024–0.031]	10.9
Cd	0.14	0.16 [0.15–0.16]	2.4	0.026	0.022 [0.021–0.028]	14.9
		0.15 [0.15–0.16]	2.7		0.023 [0.022–0.031]	10.8
		0.15 [0.15–0.16]	2.5		0.027 [0.019–0.029]	14.4
Co	0.14	0.15 [0.13–0.16]	5.0	0.035	0.035 [0.034–0.042]	6.2
		0.14 [0.13–0.15]	11.4		0.039 [0.038–0.043]	10.3
		0.15 [0.15–0.16]	6.1		0.039 [0.035–0.040]	6.8
Cr	0.093	0.095 [0.081–0.106]	14.6	0.41	0.46 [0.44–0.47]	6.5
		0.087 [0.083–0.126]	13.8		0.44 [0.38–0.49]	14.7
		0.105 [0.079–0.118]	14.5		0.41 [0.39–0.43]	8.0
Cu	0.14	0.13 [0.13–0.14]	8.0	17.0	16.3 [16.1–16.6]	3.7
		0.14 [0.13–0.17]	14.9		17.6 [16.2–18.9]	10.6
		0.15 [0.14–0.18]	9.3		16.2 [15.9–17.3]	5.1
Hg	0.066	0.039 [0.031–0.040]	14.9	0.17	0.15 [0.15–0.17]	4.6
		0.030 [0.027–0.042]	14.7		0.15 [0.14–0.16]	6.4
		0.034 [0.028–0.041]	14.9		0.15 [0.15–0.17]	4.9
Mn	0.099	0.098 [0.084–0.110]	6.8	0.049	0.049 [0.045–0.054]	7.1
		0.096 [0.093–0.103]	12.9		0.054 [0.045–0.059]	10.0
		0.089 [0.085–0.093]	7.8		0.053 [0.051–0.054]	7.5
Mo	0.63	0.72 [0.67–0.76]	4.8	2.9	3.3 [3.2–3.4]	3.8
		0.70 [0.63–0.73]	6.2		3.3 [3.1–3.5]	9.3
		0.68 [0.67–0.71]	5.0		3.1 [2.9–3.3]	4.8
Ni	0.27	0.27 [0.23–0.36]	12.2	0.18	0.14 [0.13–0.20]	11.5
		0.29 [0.26–0.37]	9.5		0.16 [0.13–0.17]	3.7
		0.31 [0.29–0.32]	11.9		0.16 [0.15–0.16]	10.8
Pb	0.34	0.31 [0.30–0.32]	7.0	0.80	0.64 [0.61–0.68]	3.6
		0.30 [0.24–0.33]	5.0		0.67 [0.65–0.71]	9.3
		0.30 [0.29–0.34]	6.8		0.63 [0.60–0.65]	4.6
Pt	0.0056	0.0051 [0.0050–0.0054]	4.9	0.010	0.009 [0.008–0.009]	4.3
		0.0056 [0.0050–0.0057]	10.2		0.010 [0.009–0.010]	14.9
		0.0055 [0.0053–0.0060]	5.8		0.010 [0.010–0.011]	6.5
Sb	0.015	0.016 [0.014–0.016]	6.5	0.056	0.063 [0.060–0.066]	6.5
		0.017 [0.016–0.019]	14.3		0.057 [0.050–0.060]	14.9
		0.017 [0.016–0.019]	7.8		0.057 [0.056–0.065]	8.0
Se	3.9	4.6 [4.1–5.3]	9.0	1.5	1.8 [1.6–2.0]	13.4
		4.2 [3.9–4.5]	13.3		1.8 [1.2–2.1]	14.8
		4.2 [4.0–4.6]	9.6		1.6 [1.5–1.8]	13.6
Sn	0.21	0.22 [0.20–0.24]	3.5	0.020	0.018 [0.016–0.020]	9.0
		0.24 [0.24–0.25]	13.7		0.017 [0.016–0.019]	5.2
		0.25 [0.24–0.25]	5.9		0.017 [0.016–0.020]	8.7
Te	0.21	0.21 [0.19–0.22]	4.5	0.032	0.032 [0.031–0.034]	6.1
		0.22 [0.21–0.24]	9.7		0.032 [0.029–0.035]	9.8
		0.21 [0.20–0.22]	5.4		0.029 [0.028–0.033]	6.6
Th	0.00040	0.00038 [0.00036–0.00042]	6.5	0.0013	0.0015 [0.0015–0.0016]	4.8
		0.00042 [0.0004–0.00043]	14		0.0015 [0.0014–0.0017]	6.9
		0.00037 [0.00033–0.00042]	7.9		0.00145 [0.0014–0.0015]	5.1
Tl	0.12	0.11 [0.10–0.11]	5.6	0.048	0.041 [0.040–0.042]	3.6
		0.11 [0.10–0.12]	8.3		0.044 [0.041–0.046]	7.5
		0.11 [0.11–0.12]	6.0		0.041 [0.040–0.044]	4.2
U	0.0044	0.0037 [0.0036–0.0038]	4.1	0.0020	0.0017 [0.0016–0.0020]	7.3
		0.0039 [0.0036–0.0042]	6.5		0.0018 [0.0016–0.0019]	4.2
		0.0037 [0.0036–0.0038]	4.4		0.0017 [0.0016–0.0019]	7.0
V	0.35	0.41 [0.37–0.42]	3.4	0.12	0.13 [0.13–0.14]	6.4
		0.37 [0.37–0.39]	12.5		0.13 [0.12–0.15]	3.6
		0.36 [0.35–0.37]	5.5		0.13 [0.12–0.14]	6.1
Zn	8.8	8.9 [8.5–11.2]	11.8	16.8	18.8 [15.6–22.0]	12.5
		9.2 [8.0–10.0]	6.4		19.3 [17.4–23.0]	4.0
		9.4 [8.3–10.9]	11.3		18.9 [17.2–20.0]	11.8

Table 4
Validation data for hair QC samples. The measured concentrations are presented for the three different days as the median [range] (μmol/g) from 6 replicate samples. The values of the CVs correspond to the intraday, interday and total CVs, respectively.

	Hair level 1: QM-H-Q1315			Hair level 2: QM-H-Q1406		
	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)
Ag	0.014	0.016 [0.016–0.017]	5.0	0.0029	0.0032 [0.0032–0.0033]	1.9
		0.016 [0.014–0.017]	5.2		0.0033 [0.0032–0.0034]	11.3
		0.016 [0.015–0.016]	5.1		0.0030 [0.0030–0.0031]	4.3
As	0.0081	0.0088 [0.0085–0.0098]	7.0	0.0080	0.0090 [0.0084–0.0091]	2.9
		0.0089 [0.0085–0.0106]	8.0		0.0080 [0.0076–0.0084]	14.6
		0.0085 [0.0082–0.0093]	7.1		0.0080 [0.0078–0.0082]	5.7
Ba	0.13	0.14 [0.14–0.14]	4.3	0.020	0.020 [0.019–0.021]	3.6
		0.13 [0.12–0.14]	14.5		0.019 [0.019–0.02]	5.2
		0.12 [0.12–0.13]	6.4		0.002 [0.019–0.021]	3.8
Be	0.045	0.054 [0.043–0.056]	8.7	0.027	0.031 [0.029–0.033]	3.6
		0.049 [0.047–0.055]	9.8		0.027 [0.027–0.028]	13.8
		0.047 [0.044–0.049]	8.8		0.029 [0.028–0.031]	5.9
Bi	0.0078	0.0087 [0.0086–0.0090]	3.1	0.0029	0.0032 [0.0031–0.0035]	4.2
		0.0080 [0.0077–0.0084]	14.6		0.0029 [0.0028–0.0031]	12.0
		0.0078 [0.0076–0.0082]	6.0		0.0031 [0.0030–0.0032]	5.7
Cd	0.018	0.019 [0.019–0.020]	3.9	0.014	0.014 [0.014–0.015]	3.0
		0.018 [0.017–0.002]	11.9		0.014 [0.014–0.015]	3.5
		0.017 [0.017–0.019]	5.5		0.014 [0.014–0.015]	3.1
Co	0.046	0.039 [0.038–0.041]	4.9	0.042	0.037 [0.036–0.038]	2.1
		0.040 [0.039–0.040]	1.5		0.037 [0.036–0.038]	0.8
		0.039 [0.036–0.045]	4.6		0.037 [0.035–0.038]	2.0
Cr	0.0087	0.0095 [0.0077–0.0096]	7.1	0.037	0.035 [0.034–0.036]	4.9
		0.0089 [0.0085–0.0094]	13.0		0.034 [0.029–0.035]	10.9
		0.0097 [0.0090–0.0104]	8.0		0.035 [0.035–0.036]	6.0
Cu	0.29	0.25 [0.24–0.26]	3.2	0.94	0.80 [0.79–0.82]	1.1
		0.25 [0.24–0.26]	3.1		0.80 [0.79–0.80]	0.9
		0.26 [0.24–0.26]	3.2		0.79 [0.79–0.81]	1.1
Hg	0.010	0.012 [0.011–0.013]	4.3	0.019	0.020 [0.020–0.021]	2.5
		0.011 [0.010–0.011]	13.8		0.020 [0.020–0.021]	3.8
		0.010 [0.010–0.011]	6.2		0.021 [0.020–0.022]	2.7
Mn	0.084	0.072 [0.069–0.073]	4.3	0.10	0.085 [0.084–0.086]	1.2
		0.074 [0.071–0.078]	5.6		0.085 [0.083–0.086]	1.3
		0.070 [0.067–0.078]	4.4		0.085 [0.085–0.087]	1.2
Mo	0.0087	0.0100 [0.0100–0.0110]	5.3	0.0038	0.0037 [0.0035–0.0039]	8.4
		0.0093 [0.0085–0.0099]	13.9		0.0036 [0.0043–0.0041]	13.8
		0.0091 [0.0084–0.0094]	6.9		0.0041 [0.0035–0.0046]	9.2
Ni	0.022	0.020 [0.018–0.02]	3.1	0.12	0.111 [0.109–0.114]	2.0
		0.018 [0.018–0.02]	4.0		0.111 [0.108–0.112]	1.9
		0.019 [0.019–0.02]	3.2		0.111 [0.105–0.112]	2.0
Pb	0.0074	0.0080 [0.0079–0.0082]	3.5	0.015	0.015 [0.014–0.015]	2.5
		0.0075 [0.0071–0.0080]	9.2		0.014 [0.013–0.014]	7.0
		0.0076 [0.0074–0.0082]	4.6		0.015 [0.014–0.015]	3.3
Pt	0.000087	0.000096 [0.000094–0.000098]	4.9	0.0012	0.0012 [0.0011–0.0012]	2.0
		0.000087 [0.000080–0.000093]	14.6		0.0011 [0.0011–0.0012]	8.6
		0.000087 [0.000082–0.000091]	6.8		0.0012 [0.0012–0.0013]	3.5
Sb	0.0076	0.0089 [0.0079–0.0092]	5.9	0.010	0.011 [0.010–0.011]	5.1
		0.0085 [0.0078–0.0093]	7.0		0.010 [0.010–0.011]	7.8
		0.0081 [0.0080–0.0088]	6.0		0.010 [0.010–0.011]	5.5
Se	0.038	0.041 [0.039–0.045]	5.6	0.013	0.012 [0.012–0.015]	5.7
		0.041 [0.039–0.046]	5.5		0.012 [0.012–0.012]	14.8
		0.044 [0.043–0.046]	5.6		0.014 [0.013–0.014]	7.5
Sn	0.050	0.069 [0.067–0.072]	4.7	0.052	0.073 [0.069–0.077]	3.2
		0.066 [0.062–0.069]	11.8		0.071 [0.070–0.073]	5.9
		0.063 [0.059–0.068]	6.0		0.074 [0.072–0.078]	3.6
Te	0.0042	0.0048 [0.0047–0.0048]	4.9	0.0055	0.0062 [0.0061–0.0063]	2.3
		0.0045 [0.0040–0.0048]	14.4		0.0058 [0.0056–0.0061]	10.5
		0.0041 [0.0041–0.0046]	6.7		0.0057 [0.0056–0.0060]	4.2
Th	0.011	0.017 [0.016–0.018]	5.4	0.023	0.029 [0.027–0.031]	2.8
		0.016 [0.015–0.017]	13.6		0.030 [0.030–0.031]	7.8
		0.016 [0.015–0.017]	6.9		0.029 [0.028–0.029]	3.7
Tl	0.0011	0.0012 [0.0011–0.0012]	4.4	0.00045	0.00049 [0.00047–0.00049]	1.9
		0.0011 [0.0010–0.0012]	13.6		0.00047 [0.00046–0.00048]	5.1
		0.0011 [0.0010–0.0011]	6.4		0.00047 [0.00046–0.00047]	2.5
U	0.0021	0.0025 [0.0023–0.0025]	5.0	0.0015	0.0016 [0.0016–0.0017]	2.3
		0.0024 [0.0023–0.0026]	9.0		0.0016 [0.0016–0.0017]	0.3
		0.0023 [0.0021–0.0025]	5.6		0.0016 [0.0016–0.0017]	2.1
V	0.024	0.020 [0.020–0.021]	4.5	0.014	0.012 [0.012–0.013]	5.4
		0.020 [0.020–0.022]	1.6		0.012 [0.011–0.014]	1.1
		0.019 [0.019–0.022]	4.2		0.012 [0.012–0.012]	5.1
Zn	3.4	3.7 [3.6–3.9]	2.8	4.9	5.0 [4.9–5.1]	3.3
		3.8 [3.6–4.0]	3.5		4.9 [4.8–5.2]	5.5
		3.7 [3.6–3.7]	2.9		5.2 [4.8–5.4]	3.6

Table 5
Validation data for internal QC samples. The measured concentrations are presented for the three different days as the median [range] (μM) from 6 replicate samples. The values of the CVs correspond to the intraday, interday and total CVs, respectively.

	Internal QC level 1			Internal QC level 2			Internal QC level 3		
	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)
Ag	0.75	0.47 [0.47–0.48]	1.7	2.5	2.4 [2.3–2.4]	2.0	7.5	7.8 [7.3–8.8]	10.9
		0.45 [0.44–0.47]	6.1		2.6 [2.5–2.6]	14		7.9 [6.2–8.2]	10.7
		0.46 [0.45–0.47]	2.7		2.7 [2.6–2.7]	5.3		7.1 [6.0–7.9]	10.9
As	0.075	0.083 [0.077–0.095]	7.8	0.25	0.29 [0.26–0.30]	11.5	0.75	0.86 [0.79–0.93]	9.9
		0.086 [0.078–0.092]	14.6		0.31 [0.22–0.33]	1.8		0.90 [0.71–1.00]	1.1
		0.075 [0.069–0.087]	9.0		0.29 [0.25–0.31]	10.8		0.87 [0.76–0.91]	9.2
Au	0.075	0.073 [0.068–0.075]	4.0	0.25	0.23 [0.20–0.30]	9.9	0.75	0.80 [0.78–0.84]	3.9
		0.068 [0.067–0.071]	10.5		0.25 [0.24–0.26]	8.3		0.79 [0.77–0.80]	11.5
		0.069 [0.060–0.070]	5.2		0.26 [0.22–0.26]	9.7		0.72 [0.68–0.80]	5.5
Ba	0.38	0.40 [0.38–0.41]	2.8	1.3	1.3 [1.2–1.3]	3.2	3.8	3.9 [3.8–4.0]	4.0
		0.41 [0.40–0.42]	5.3		1.3 [1.2–1.3]	4.0		3.9 [3.6–4.2]	5.6
		0.40 [0.39–0.40]	3.2		1.3 [1.2–1.3]	3.3		4.0 [3.9–4.3]	4.2
Be	0.038	0.039 [0.036–0.041]	4.7	0.13	0.12 [0.11–0.13]	4.2	0.38	0.41 [0.38–0.44]	4.9
		0.041 [0.037–0.043]	12.5		0.12 [0.12–0.13]	14.0		0.39 [0.38–0.40]	9.8
		0.042 [0.042–0.046]	6.2		0.13 [0.13–0.13]	6.2		0.37 [0.35–0.40]	5.7
Bi	0.075	0.080 [0.079–0.083]	1.5	0.25	0.27 [0.26–0.27]	2.6	0.75	0.73 [0.72–0.75]	3.0
		0.078 [0.076–0.079]	6.6		0.26 [0.25–0.26]	9.6		0.73 [0.69–0.76]	8.4
		0.076 [0.075–0.078]	2.7		0.25 [0.23–0.25]	4.1		0.77 [0.76–0.80]	4.0
Cd	0.75	0.75 [0.72–0.77]	1.9	2.5	2.5 [2.3–2.5]	2.9	7.5	7.0 [6.8–7.2]	3.8
		0.74 [0.72–0.76]	5.5		2.4 [2.3–2.4]	5.0		7.0 [6.6–7.4]	4.6
		0.72 [0.71–0.73]	2.6		2.4 [2.2–2.4]	3.2		7.2 [6.9–7.5]	3.9
Ce	0.075	0.075 [0.074–0.077]	1.5	0.25	0.26 [0.25–0.27]	4.2	0.75	0.78 [0.73–0.83]	3.7
		0.077 [0.075–0.078]	2.1		0.26 [0.26–0.29]	8.1		0.79 [0.78–0.81]	3.1
		0.075 [0.074–0.077]	1.6		0.26 [0.24–0.26]	4.8		0.79 [0.76–0.83]	3.6
Co	1.5	1.6 [1.6–1.7]	1.8	5.0	5.6 [5.4–5.7]	2.4	15.0	16.3 [15.0–17.4]	4.2
		1.7 [1.7–1.8]	8.4		5.6 [5.6–5.8]	1.9		16.1 [15.5–16.9]	6.2
		1.7 [1.7–1.8]	3.3		5.7 [5.5–5.9]	2.3		16.9 [16.4–17.4]	4.5
Cr	0.75	0.72 [0.71–0.74]	2.1	2.5	2.4 [2.4–2.5]	2.4	7.5	7.3 [7.1–7.6]	4.1
		0.76 [0.73–0.78]	11.1		2.5 [2.5–2.6]	5.0		7.5 [6.9–8.0]	3.2
		0.78 [0.76–0.82]	4.3		2.6 [2.5–2.6]	2.8		7.4 [7.1–7.5]	4.0
Cs	0.075	0.087 [0.080–0.088]	3.7	0.25	0.29 [0.26–0.30]	3.4	0.75	0.82 [0.79–0.88]	3.1
		0.088 [0.080–0.090]	1.3		0.28 [0.28–0.29]	5.5		0.85 [0.84–0.87]	5.0
		0.085 [0.084–0.086]	3.5		0.28 [0.26–0.28]	3.7		0.86 [0.81–0.90]	3.4
Cu	15.0	15.8 [15.4–15.9]	1.9	50	53 [53–56]	2.3	150	158 [150–163]	4.0
		16.9 [16.4–17.6]	11.7		53 [52–55]	2.6		157 [143–165]	4.3
		17.1 [16.9–17.6]	4.4		53 [51–54]	2.4		160 [156–165]	4.1
Fe	37.5	39.0 [37.2–40.1]	2.2	125	130 [128–135]	2.2	375	366 [329–391]	5.2
		40.1 [39.1–41.8]	6.8		131 [130–138]	2.7		342 [316–360]	10.2
		41.1 [40.3–41.7]	3.1		133 [130–139]	2.2		365 [357–386]	6.1
Ge	0.075	0.082 [0.070–0.095]	7.6	0.25	0.27 [0.26–0.29]	4.3	0.75	0.84 [0.69–1.00]	9.9
		0.086 [0.080–0.090]	5.1		0.29 [0.28–0.29]	9.1		0.87 [0.69–0.97]	3.0
		0.082 [0.078–0.088]	7.2		0.29 [0.26–0.30]	5.1		0.86 [0.75–0.89]	9.3
Hf	0.075	0.092 [0.062–0.096]	9.5	0.25	0.29 [0.23–0.33]	12.8	0.75	0.82 [0.74–0.90]	5.4
		0.086 [0.080–0.091]	3.7		0.29 [0.22–0.29]	5.0		0.84 [0.75–0.86]	4.2
		0.084 [0.077–0.088]	9.0		0.29 [0.22–0.29]	12.2		0.85 [0.82–0.90]	5.3
Hg	0.75	0.87 [0.83–0.87]	1.6	2.5	2.9 [2.8–2.9]	1.2	7.5	7.4 [7.0–7.4]	4
		0.84 [0.82–0.85]	3.6		2.9 [2.8–2.9]	14.9		7.6 [7.0–8.0]	5.5
		0.85 [0.83–0.86]	2.0		2.6 [2.5–2.6]	5.2		7.5 [7.3–7.9]	4.2
La	0.075	0.069 [0.068–0.072]	1.6	0.25	0.24 [0.23–0.25]	3.1	0.75	0.73 [0.71–0.74]	4.1
		0.071 [0.068–0.072]	1.9		0.25 [0.24–0.26]	6.4		0.71 [0.67–0.76]	5.2
		0.070 [0.068–0.071]	1.7		0.24 [0.22–0.24]	3.7		0.75 [0.70–0.78]	4.2
Mn	0.15	0.17 [0.15–0.18]	6.1	0.50	0.58 [0.52–0.60]	4.5	1.5	1.7 [1.6–1.8]	2.7
		0.17 [0.16–0.18]	5.1		0.58 [0.52–0.60]	2.1		1.7 [1.7–1.8]	1.9
		0.17 [0.16–0.18]	6.0		0.57 [0.56–0.60]	4.3		1.7 [1.7–1.8]	2.6
Mo	0.11	0.11 [0.10–0.11]	3.7	0.38	0.35 [0.32–0.37]	3.7	1.1	1.1 [1.0–1.2]	4.5
		0.11 [0.11–0.12]	7.7		0.35 [0.34–0.36]	0.9		1.1 [1.0–1.1]	1.8
		0.11 [0.11–0.11]	4.4		0.35 [0.34–0.36]	3.5		1.1 [1.0–1.2]	4.3
Ni	3.8	3.7 [3.7–3.8]	1.6	12.5	12.6 [12.4–13.1]	2.5	37.5	36.4 [35.7–38.0]	3.9
		3.8 [3.7–3.9]	7.7		12.3 [12.2–12.9]	6.5		39.2 [36.1–41.4]	7.2
		4.0 [3.9–4.0]	3.0		13.1 [12.5–13.6]	3.2		38.5 [37.4–39.5]	4.4
Pb	0.38	0.38 [0.38–0.39]	1.5	1.3	1.2 [1.1–1.2]	2.6	3.8	3.4 [3.3–3.5]	3.5
		0.35 [0.34–0.36]	13.3		1.2 [1.1–1.2]	2.3		3.5 [3.3–3.7]	10.3
		0.35 [0.34–0.36]	4.8		1.2 [1.1–1.2]	2.5		3.2 [3.1–3.4]	4.8
Pd	0.033	0.028 [0.026–0.031]	6.7	0.11	0.10 [0.09–0.10]	6.0	0.38	0.32 [0.30–0.37]	9.6
		0.028 [0.026–0.030]	10.1		0.10 [0.09–0.10]	5.7		0.34 [0.29–0.38]	5.1
		0.030 [0.028–0.034]	7.2		0.10 [0.09–0.11]	6.0		0.31 [0.29–0.39]	9.2
Pt	0.0075	0.0085 [0.0082–0.0086]	1.8	0.025	0.029 [0.028–0.029]	2.2	0.075	0.083 [0.079–0.089]	3.5
		0.0086 [0.0083–0.0088]	2.5		0.029 [0.028–0.029]	3.5		0.083 [0.082–0.083]	1.3
		0.0086 [0.0085–0.0088]	1.9		0.028 [0.027–0.029]	2.4		0.083 [0.081–0.087]	3.3

(continued on next page)

Table 5 (*continued*)

	Internal QC level 1			Internal QC level 2			Internal QC level 3		
	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)	Theoretical concentration	Measured concentration	CV (%)
Rb	3.8	4.0 [3.8–4.2]	2.7	12.5	14.3 [13.7–14.4]	2.9	37.5	35.0 [32.0–36.9]	4.9
		4.0 [3.8–4.1]	6.0		12.8 [12.5–13.4]	14.0		33.5 [32.3–34.4]	5.1
		4.2 [4.1–4.3]	3.3		14.5 [13.5–14.7]	5.5		33.8 [30.0–35.1]	4.9
Ru	0.00075	0.00082 [0.00081–0.00085]	2.3	0.0025	0.0024 [0.0024–0.0025]	3.2	0.0075	0.0077 [0.0073–0.0084]	4.0
		0.00076 [0.00072–0.00077]	14.8		0.0025 [0.0025–0.0026]	5.6		0.0080 [0.0077–0.008]	2.8
		0.00073 [0.00071–0.00076]	5.5		0.0025 [0.0023–0.0026]	3.6		0.0077 [0.0074–0.0081]	3.9
Se	0.75	0.94 [0.86–1.00]	4.2	2.5	2.9 [2.7–3.1]	4.4	7.5	9.1 [8.1–9.7]	5.5
		0.97 [0.92–1.01]	5.9		3.1 [2.8–3.1]	7.4		8.9 [8.6–9.6]	10.1
		0.93 [0.88–0.98]	4.4		2.9 [2.7–3.1]	4.9		8.4 [7.9–8.7]	6.3
Sr	0.75	0.78 [0.77–0.81]	1.7	2.5	2.7 [2.6–2.8]	3.5	7.5	8.4 [7.8–8.9]	4.0
		0.81 [0.79–0.83]	4.6		2.8 [2.7–2.9]	4.6		8.4 [8.3–8.6]	3.8
		0.81 [0.80–0.83]	2.2		2.8 [2.6–2.8]	3.6		8.1 [7.8–8.7]	3.9
Te	0.0038	0.0043 [0.0038–0.0047]	8.6	0.013	0.014 [0.013–0.016]	6.2	0.038	0.046 [0.038–0.047]	7.7
		0.0044 [0.0037–0.0045]	0.7		0.014 [0.013–0.015]	1.1		0.043 [0.037–0.045]	3.3
		0.0041 [0.0038–0.0049]	8.1		0.014 [0.013–0.015]	5.8		0.042 [0.041–0.045]	7.3
Th	0.00075	0.00081 [0.00077–0.00085]	2.9	0.0025	0.0029 [0.0025–0.0029]	5.4	0.0075	0.0078 [0.0077–0.0078]	3.6
		0.00074 [0.00073–0.00076]	14.3		0.0027 [0.0026–0.0027]	8.8		0.0080 [0.0075–0.0086]	5.3
		0.00073 [0.0007–0.00076]	5.6		0.0026 [0.0024–0.0028]	5.9		0.0076 [0.0075–0.0082]	3.9
Ti	0.75	0.74 [0.73–0.75]	2.0	2.5	2.5 [2.4–2.6]	3.0	7.5	7.3 [7.2–7.4]	3.5
		0.74 [0.73–0.76]	3.2		2.5 [2.4–2.5]	5.0		7.3 [6.8–7.8]	2.8
		0.72 [0.71–0.75]	2.1		2.4 [2.3–2.5]	3.3		7.4 [7.4–7.6]	3.4
Tl	0.0038	0.0038 [0.0036–0.0040]	3.4	0.013	0.013 [0.013–0.014]	3.8	0.038	0.042 [0.040–0.045]	4.3
		0.0043 [0.0042–0.0043]	15		0.015 [0.013–0.015]	9.1		0.043 [0.042–0.044]	2.8
		0.0042 [0.0039–0.0044]	6.2		0.014 [0.014–0.015]	4.8		0.043 [0.039–0.045]	4.1
U	0.000075	0.000073 [0.000066–0.000079]	6.5	0.00025	0.00027 [0.00027–0.00031]	5.2	0.00075	0.00078 [0.00073–0.00082]	3.8
		0.000070 [0.000066–0.000072]	9.9		0.00026 [0.00025–0.00028]	12.3		0.00078 [0.00078–0.00080]	11.8
		0.000076 [0.000068–0.000085]	7.0		0.00026 [0.00025–0.00027]	6.4		0.00085 [0.00081–0.00089]	5.4
V	0.11	0.12 [0.12–0.13]	4.1	0.38	0.38 [0.37–0.43]	4.2	1.1	1.2 [1.1–1.2]	4.2
		0.13 [0.12–0.13]	6.3		0.40 [0.39–0.41]	3.9		1.2 [1.1–1.3]	6.3
		0.13 [0.12–0.13]	4.4		0.41 [0.39–0.42]	4.2		1.1 [1.1–1.2]	4.5
W	0.075	0.078 [0.076–0.079]	1.6	0.25	0.26 [0.25–0.27]	2.1	0.75	0.71 [0.71–0.72]	3.2
		0.076 [0.075–0.078]	4.9		0.25 [0.24–0.25]	7.8		0.73 [0.68–0.76]	7.5
		0.075 [0.073–0.076]	2.2		0.25 [0.24–0.25]	3.3		0.76 [0.74–0.79]	3.9
Zn	15.0	13.6 [13.0–13.9]	2.3	50	47 [46–50]	3.1	150	144 [132–153]	4.4
		15.0 [14.7–15.6]	14.8		48 [48–51]	3.4		147 [137–153]	5.9
		15.0 [14.5–15.2]	5.5		48 [46–50]	3.2		147 [145–155]	4.6
Zr	0.0075	0.0085 [0.0079–0.0090]	10.0	0.025	0.038 [0.037–0.04]	3.3	0.075	0.076 [0.07–0.079]	7.0
		0.0091 [0.0071–0.0097]	1.7		0.038 [0.038–0.041]	2.0		0.078 [0.069–0.085]	8.6
		0.0090 [0.0075–0.0093]	9.4		0.039 [0.036–0.04]	3.2		0.080 [0.076–0.086]	7.2

acquisition parameters (2 runs, 2 passes, and the sample parameters described in Supplementary Table 2), the total run time was 3.8 min per sample, and the sample volume was 2 mL.

3.3. Validation of the method

The LLOQ and calibration curve were selected to cover the range of concentrations described in human whole blood, urine or hair samples [3,7,13–16]. The LLOQ and ULOQ for each element are given in Table 1. Some of the elements analysed here (such as U, Ru and Hf) are not at all abundant in human samples (i.e. pM concentrations), while others (such as Cu and Zn) are quite abundant (μM concentrations). Hence, the dynamic range was different for each element (from 1.3- to 7.0-log), with LLOQ ranging from 0.1 pM (Hf) to 10 μM (Zn). The regression was linear for all elements other than ^{205}Tl, for which quadratic regression was used. The correlation coefficient for calibration curves (analysed on 6 different days) ranged from 0.9963 to 0.9999. For each element, the LLOQ, ULOQ, number of calibration standards, and the calibration curve's slope, y-intercept and correlation coefficient are shown in Table 1.

The measured concentrations and precision for the intraday and interday analysis of external QC samples (whole blood, urine and hair) and internal QC samples are detailed in Tables 2–5. The intraday, interday or total precision was always below 15%. The method developed here was therefore highly precise for the determination of all 38 tested elements over a wide range of concentrations and in all matrices.

3.4. Analysis of clinical trial samples

The results for samples from 25 clinical trial participants are shown in the Figure. The method was suitable for the analysis of clinical samples of whole blood, hair or lung tissue (Fig. 1).

4. Conclusion

Here, we describe a method for the quantification of metals and metalloids in human samples of whole blood, urine, hair and tissues. The method has a number of advantages over previously described methods: the simultaneous analysis of 38 elements, microwave mineralization, high sensitivity, high precision, and a broad dynamic range that can be customized for each element. Furthermore, the method was found to be suitable for the analysis of human samples from clinical trial participants over the whole concentration range reported in these matrices.

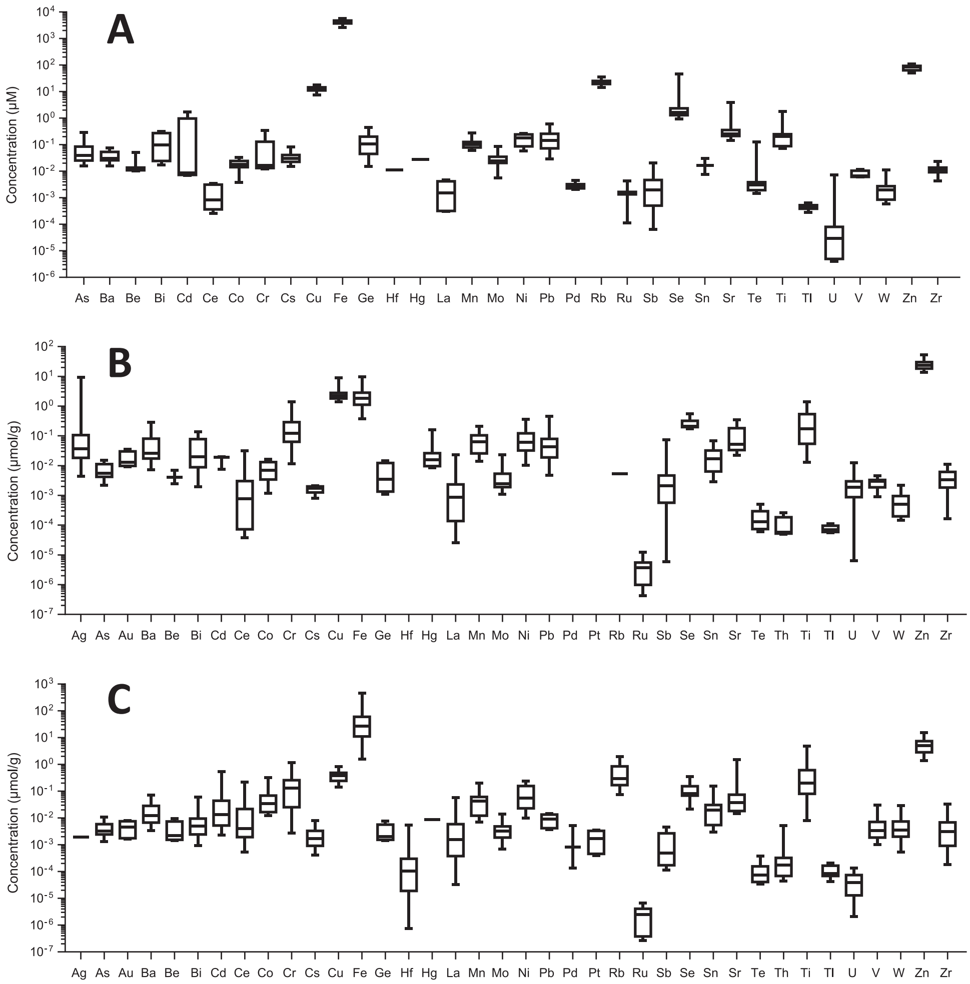

Fig. 1. Concentrations of elements in (A) whole blood (µM), (B) hair (µmol/g) and (C) lung tissue (µmol/g) samples from 25 participants in a lung cancer clinical trial. The whiskers indicate the range of values, and the horizontal line indicates the mean.

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Disclosure of conflicts of interest

The authors declare no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.talanta.2019.02.068.

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