CCQM-K139

Elements in Human Serum

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Final Report

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Abstract

Elements in serum serve as important biomarkers and reflect the well-being of an individual. The Key Comparison CCQM-K139 (Elements in human serum) aimed to enable participating National Metrology Institutes (NMIs) and Designated Institutes (DIs) to demonstrate their competence in the determination of elements (electrolytes and essential elements) in human serum. This is in line with the IAWG's five year plan that a comparison under the Measurement Category 10 (Biological Fluids and Materials) is organised in order to best cover current and future CMCs.

Table A summarises the list of measurands covered in this comparison, as well as the list of NMIs/DIs that registered and submitted their results for each measurand.

Table A. List of measurands and the number of participating NMIs/DIs for the respective measurand

Measurand	Number of registered institutes	Participating NMIs/DIs
Na	10	NIM, LNE, PTB, GLHK, KRISS, INM, HSA, TUBITAK UME, LGC and LATU
Cl	8	NIM, LNE, PTB, KRISS, INM, HSA, TUBITAK UME and NIST
Cu	11	NMIA, BIM, NIM, PTB, GLHK, KRISS, INM, HSA, TUBITAK UME, LATU and NIST
Se	6	NMIA, KRISS, INM, HSA, TUBITAK UME and LATU
P	8	NIM, KRISS, INM, HSA, TUBITAK UME, LGC, LATU and NIST

For the analysis of sodium, copper, selenium and phosphorus, most of the participating institutes employed microwave-assisted digestion and acid digestion (with or without heating) sample dissolution. For the analysis of chloride, in addition to the microwave-assisted digestion and acid digestion, a wider variety of techniques were employed. These included matrix separation, alkaline extraction and coulometric titration. For sodium and phosphorus, inductively coupled plasma mass spectrometry (ICP-MS) and inductively coupled plasma

optical emission spectrometry (ICP-OES) were the two most commonly used instrumental techniques. Other techniques used included ion chromatography (IC) and flame atomic absorption spectrometry (FAAS). For chloride, copper and selenium, the most widely used instrumental technique was ICP-MS. Other techniques used included IC, titration, micro-coulometry and ICP-OES. In this key comparison, the participating institutes have demonstrated the inorganic core capabilities in human serum matrix as listed in Table B.

Table B. List of measurands and the inorganic core capabilities demonstrated by the NMIs/DIs for the respective measurand

Inorganic core capability	**Measurand**	**Participating NMIs/DIs**
ID-ICP-MS	Cl	KRISS and HSA
	Cu	NMIA, PTB, KRISS, HSA, TUBITAK UME, LATU and NIST
	Se	NMIA, KRISS, HSA, TUBITAK UME and LATU
ICP-MS (without isotope dilution)	Na	LNE, INM, HSA and TUBITAK UME
	Cl	LNE, INM and TUBITAK UME
	Cu	BIM, NIM, GLHK and INM
	Se	INM
	P	INM, HSA, TUBITAK UME, LGC, LATU and NIST
ICP-OES	Na	GLHK, KRISS, LGC and LATU
	Cu	GLHK
	P	NIM and KRISS
IC	Na	PTB
	Cl	NIM
Titration	Cl	PTB
Micro-coulometry	Cl	NIST
FAAS	Na	NIM

Table of Content

1. Introduction

Elements in serum serve as important biomarkers and reflect the well-being of an individual. Electrolytes such as sodium (Na) and chloride (Cl) are commonly measured since they play a central role in maintaining the normal distribution of water, the osmotic pressure and the electrical neutrality in the body. Trace element such as copper (Cu) is involved in many oxidation-reduction reactions and metalloenzymes. The majority of selenium (Se) occurs in the form of selenoproteins that serve as cofactors in the glutathione peroxidase activity, which plays a major role in protection against free radicals. Phosphorus (P) is the second most abundant element in the body after calcium. Both elements are required for strong bones and teeth. Phosphorus, on its own, is indispensable for growth, maintenance and repair of tissues and cells.

At the IAWG meeting in October 2014, the Health Sciences Authority (HSA), Singapore proposed to organise a comparison for the determination of elements in human serum in 2017. In the IAWG's five year plan, a comparison under the Measurement Category 10 (Biological Fluids and Materials) was proposed in order to best cover current and future CMCs. After conducting a survey and further discussions at the IAWG meeting in November 2015, the elements (Na, Cl, Cu, Se and P) were chosen to be covered in CCQM-K139 and P173: Elements in human serum. These elements were not covered in the last two comparisons in the clinical area [CCQM-K14: Ca in serum and CCQM-K107 & P146: Elements (K, Ca, Mg, Fe) and selenomethionine in human serum] and offered different analytical challenges.

The comparison aimed to enable participating National Metrology Institutes (NMIs) and Designated Institutes (DIs) to demonstrate their competence in the determination of elements (electrolytes and essential elements) in human serum. It also enabled NMIs/DIs with the relevant services to submit Calibration and Measurement Capability (CMC) claims upon successful completion. Participating institutes were requested to complete the Inorganic Core Capabilities Tables as supporting evidence for their CMC claims.

2. Participating Institutes

A total of 13 institutes registered for CCQM-K139 key comparison. Table 1 lists the participating institutes in alphabetical order of the countries.

Table 1. List of participating NMIs/DIs, countries, contact persons and measurand registered

No.	Participating NMI/DI	Country	Contact person	Measurand
1	NMIA National Measurement Institute, Australia	Australia	David Saxby, Paul Armishaw	Cu, Se
2	BIM Bulgarian Institute of Metrology	Bulgaria	Veronika Ivanova	Cu
3	NIM National Institute of Metrology, P. R. China	China	Feng Liuxing, Wang Jun	Na, Cl, Cu, P
4	LNE Laboratoire National de Métrologie et d'essais	France	M. Estela del Castillo Busto, Paola Fisicaro	Na, Cl
5	PTB Physikalisch-Technische Bundesanstalt	Germany	Olaf Rienitz	Na, Cl, Cu
6	GLHK Government Laboratory, Hong Kong	Hong Kong SAR, China	Wai-hong Fung, Michael Ho-pan Yau	Na, Cu
7	KRISS Korea Research Institute of Standards and Science	Korea	Yong-Hyeon Yim	Na, Cl, Cu, Se, P
8	INM National Institute of Metrology	Romania	Mirella Buzoianu	Na, Cl, Cu, Se, P

No.	Participating NMI/DI	Country	Contact person	Measurand
9	HSA Health Sciences Authority	Singapore	Richard Shin	Na, Cl, Cu, Se, P
10	TUBITAK UME National Metrology Institute of Turkey	Turkey	Suleyman Z. Can	Na, Cl, Cu, Se, P
11	LGC LGC Limited	UK	Heidi Goenaga Infante	Na, P
12	LATU Laboratorio Tecnológico del Uruguay	Uruguay	Ramiro Pérez-Zambra, Elizabeth Ferreira	Na, Cu, Se, P
13	NIST National Institute of Standards and Technology	USA	Stephen Long	Cl, Cu, P

3. Samples and Instructions to Participating Institutes

3.1. Materials

The comparison material was human serum. An experienced commercial human blood products supplier (Solomon Park Research Laboratories, Kirkland, WA, USA) was engaged by HSA to prepare the material. One pool of human serum material was prepared and pre-packed in 200 vials containing 3 mL of serum each.

The expected mass fractions of the measurands in the study material are listed in Table 2. The concentration levels were within the normal biological range and within the range of existing CMC claims in the International Bureau of Weights and Measures' Key Comparison Database (BIPM KCDB).

Table 2. Expected mass fractions of the measurands in the study material

Measurand	Expected mass fraction (mg/kg)
Na	2500 – 4000
Cl	3000 – 5000
Cu	0.1 – 5.0
Se	0.03 – 0.30
P	80 – 150

3.2. Homogeneity and Stability Studies

The homogeneity of the elements in the comparison material was assessed by inductively coupled plasma mass spectrometry (ICP-MS). A sample size of 0.10 g was used in the assessment of homogeneity. Eleven bottles were randomly and stratifically selected, and two subsamples were taken from each bottle. Using ANOVA at 95 % level of confidence, the material was found to be sufficiently homogeneous. The standard uncertainties of inhomogeneity (u_{bb}) were calculated using Equation 1 in accordance with ISO Guide 35:2006 [1]. The ANOVA test results and relative standard uncertainties of inhomogeneity (u_{bb}) are summarised in Table 3.

$$u_{bb} = \sqrt{\frac{MS_{within}}{n}} \cdot \sqrt[4]{\frac{2}{v_{MS_{within}}}} \quad (1)$$

where:

u_{bb} = standard uncertainties of inhomogeneity

MS_{within} = mean square within bottle variance

$v_{MSwithin}$ = degree of freedom of MS_{within}

n = number of replicates

Table 3. ANOVA test results and relative standard uncertainties of inhomogeneity of the comparison material

Measurand	ANOVA test		Relative standard uncertainties of inhomogeneity, u_{bb} (%)
	F-statistics	F-critical	
Na	1.31	2.85	0.11
Cl	1.61	2.85	0.41
Cu	0.86	2.85	0.22
Se	1.43	2.85	0.64
P	0.43	2.85	0.44

The stability of the elements at -20 ± 10 °C in the comparison material was assessed by ICP-MS. A short-term stability study using isochronous design was carried out over a period of 8 weeks. Two randomly selected bottles were transferred from the reference temperature of -80 ± 10 °C to -20 ± 10 °C on five occasions over the study period. One subsample was then taken from each bottle. Using Student's *t*-test on the slope of the linear regression at 95 % level of confidence, no significant instability of the elements in the comparison material was observed (Figure 1). Table 4 summarises the Student's *t*-test results.

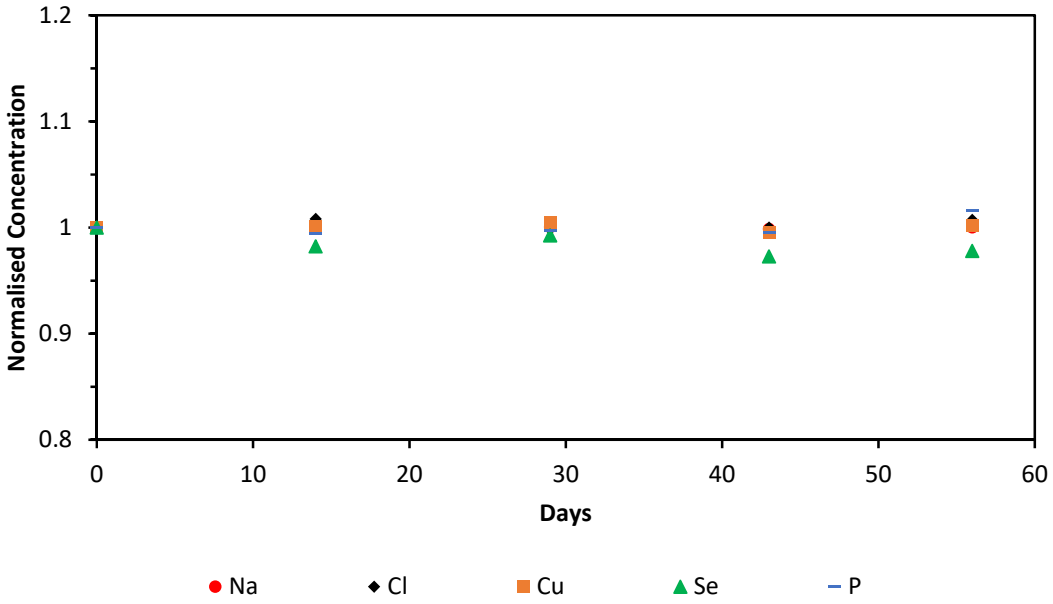

Figure 1. Results from the short-term stability study

The long-term stability of the elements in the comparison material at -80 ± 10 °C was assessed using ICP-MS. The testings were carried out on four occasions over a period of about 13 months using classical design. On each occasion of the stability testing, two bottles were randomly selected and one subsample was taken from each bottle. Student's *t*-test on the slope of the linear regression at 95 % level of confidence was used for the evaluation of instability of the elements in the comparison material. No instability was observed during the duration of the comparison at the recommended storage temperature (-80 °C) (Figure 2). The Student's *t*-test results are summarised in Table 4.

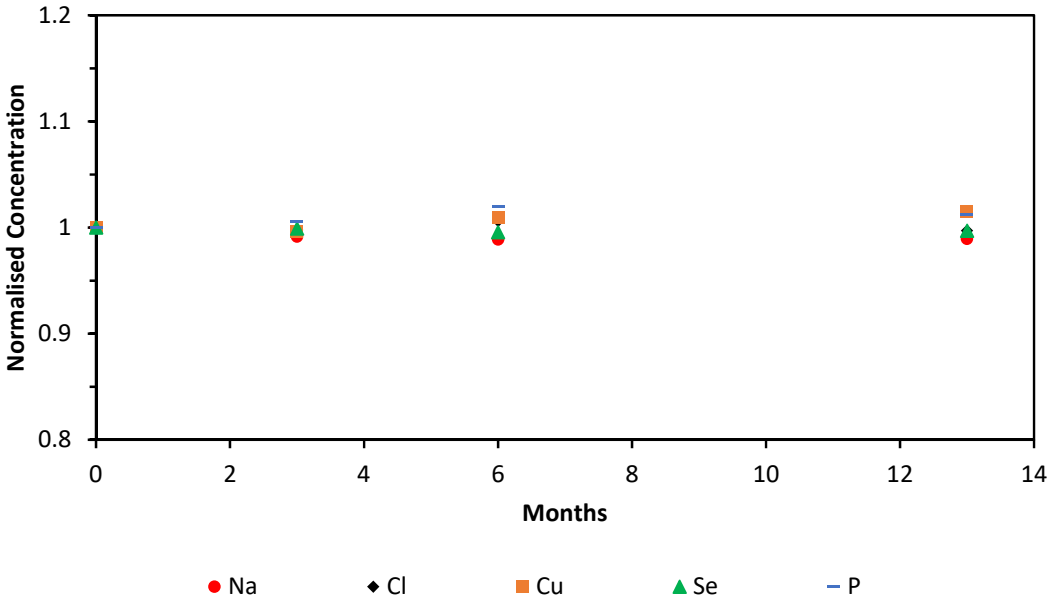

Figure 2. Results from the long-term stability study

Table 4. Student's *t*-test results of short-term and long-term stabilities for the comparison material

Measurand	Short-term stability		Long-term stability	
	Student's *t*-test		Student's *t*-test	
	t-calculated	*t*-critical	*t*-calculated	*t*-critical
Na	0.66	3.18	1.49	4.30
Cl	0.36	3.18	0.31	4.30
Cu	0.27	3.18	2.77	4.30
Se	2.05	3.18	1.32	4.30
P	1.24	3.18	1.06	4.30

3.3. Instructions to Participating Institutes

The material used for this comparison was tested non-reactive/negative for hepatitis B surface antigen (HbsAg), human immunodeficiency (HIV) 1 and 2 antibodies, and hepatitis C virus (HCV) by the supplier before distribution. However, the material was required to be handled as biohazards material capable of transmitting infectious diseases.

The comparison samples were transported in dry ice. It was instructed that upon receipt, the samples should be immediately stored at below -60 °C for long-term storage. A freezer

temperature of -20 °C was also acceptable for storage up to 8 weeks. The material was meant to be used as soon as possible after it was thawed.

Each participating NMI/DI received between two to six bottles of serum material depending on the number of measurands it registered for, e.g. a NMI/DI received a total of 6 bottles if it registered for all 5 measurands. The participating NMIs/DIs were free to decide on the number of times that each subsample was to be measured. Before sampling, the sample should be thawed and warmed to room temperature (18 – 25 °C), and homogenised by gentle swirling and inversing the bottle several times. The recommended minimum subsample size was 0.10 g. The participating NMIs/DIs was expected to use their own methods for the determination. Metrologically traceable certified reference materials (CRMs) were required to be used as calibration standards.

A Report of Results Form was provided to the participating NMIs/DIs for completion. The participating institutes were requested to report their results based on the measurement of at least five subsamples for each measurand. The results were reported in the unit of mg/kg, and included standard and expanded uncertainties (95 % level of confidence) for the mean of the replicate determinations. The participating NMIs/DIs were also asked to include information on the measurement procedure, calibration standard, internal standard, quality control material, calculation of the results, and estimation of measurement uncertainty. The completed Results Form and the Core Capability Table were to be sent to HSA on or before the scheduled deadline.

4. Methods of Measurement

Table 5 summarises the measurement methods used by the participating NMIs/DIs for CCQM-K139.

Table 5. Measurement methods used by the participating NMIs/DIs

Participating NMI/DI	Measurand	Dissolution method	Calibration method	Analytical instrument	Reference material used for calibration (traceability)
NMIA	Cu, Se	Microwave-assisted digestion (HNO_3/H_2O_2/UHP)	Cu: Exact-matching IDMS ($^{65}Cu/^{63}Cu$) Se: Exact-matching IDMS ($^{80}Se/^{74}Se$)	Cu: ICP-SF-MS (confirmation by ICP-MS-Q-MS) Se: ICP-MS-Q-MS (confirmation by ICP-SF-MS)	Cu: NIST SRM 3114 Copper standard solution (Lot no. 121207) Se: NIST SRM 3149 Selenium standard solution (Lot no. 100901)
BIM	Cu	Acid dilution	External calibration (^{65}Cu)	ICP-MS	NIST SRM 3114 Copper standard solution
NIM	Na, Cl, Cu, P	Na: Acid dilution (HCl) Cl: Heating followed by dissolution with 5% HNO_3	Na: External calibration (Na589.0nm) Cl: External calibration (Cl^-) Cu: Double IDMS ($^{63}Cu/^{65}Cu$)	Na: Flame AAS Cl: IC Cu: ICP-MS P: ICP-OES	Na: GBW(E)080127 Cl: GBW(E)080268 Cu: GBW08615 P: GBW(E)080431

Participating NMI/DI	Measurand	Dissolution method	Calibration method	Analytical instrument	Reference material used for calibration (traceability)
		Cu and P: Heat-assisted acid digestion (HNO_3)	P: External calibration (P231.6)		
LNE	Na, Cl	Acid dilution	Na: Multi-point external calibration (^{23}Na) Cl: Multi-point external calibration (^{35}Cl, ^{37}Cl)	HR-ICP-MS	NIST SRM 919b
PTB	Na, Cl, Cu	Na and Cu: Microwave-assisted digestion (HNO_3/H_2O_2) Cl: Muffle furnace ($H_2O/HNO_3/NaOH$)	Na: Exact matching ion chromatography Cl: Exact matching argentometric titration (potentiometric end-point) Cu: Exact matching double IDMS	Na: Metrohm 930 Compact IC Flex Metrosep CSUPPA-250/4.0 Cl: Metrohm Titrando 888 Cu: Element XR (HR-mode)	Na and Cl: NIST SRM 919b Cu: NIST SRM 885
GLHK	Na, Cu	Heat-assisted digestion (HNO_3/H_2O_2)	Gravimetric standard addition	Na: ICP-OES Cu: ICP-OES and ICP-MS	Na: NIST SRM 3152a Cu: NIST SRM 3114

Participating NMI/DI	Measurand	Dissolution method	Calibration method	Analytical instrument	Reference material used for calibration (traceability)
KRISS	Na, Cl, Cu, Se, P	Microwave-assisted digestion (HNO_3)	Na: Exact matrix matching ICP-OES (330.237 nm) Cl: Exact-matching IDMS ($^{35}Cl^+/^{37}Cl^+$) Cu: Exact-matching IDMS ($^{63}Cu^+/^{65}Cu^+$) Se: Exact-matching IDMS ($^{82}Se^+/^{78}Se^+$) P: Exact matrix matching ICP-OES (213.617 nm)	Na and P: ICP-OES Cl and Cu: ICP-SFMS ($R \geq 9000$) Se: ICP-QQQMS ($Se^+ \rightarrow SeO^+$ with O_2 collision gas)	Na: KRISS Sodium standard solution Cl: KRISS Chloride standard solution Cu: KRISS Copper standard solution Se: KRISS Selenium standard solution P: KRISS Phosphorus standard solution
INM	Na, Cl, Cu, Se, P	Na and P: Dilution with dilute acid (1% HNO_3) Cl: Protein removal using dilute acid (5% HNO_3), precipitation using silver nitrate and followed by	Na: External calibration (bracketing ^{23}Na) Cl: External calibration ($^{107}Ag/^{103}Rh$) Cu: External calibration ($^{63}Cu/^{103}Rh$)	ICP-MS ELAN DRC 600 Perkin Elmer	Na: NIST SRM 3152a Sodium standard solution Cl: NIST SRM 3151 Silver standard solution Cu: NIST SRM 3114 Copper standard solution Se: NIST SRM 3149 Selenium standard solution

Participating NMI/DI	Measurand	Dissolution method	Calibration method	Analytical instrument	Reference material used for calibration (traceability)
		dissolution using NH_4OH Cu and Se: Dilution with a mixture of dilute TMAH (1.5%) and HCl (1.5%)	Se: Standard addition and external calibration (bracketing $^{78}Se/^{103}Rh$) P: External calibration (bracketing ^{31}P)		P: NIST SRM 3139a Phosphorus standard solution
HSA	Na, Cl, Cu, Se, P	Na: Acid digestion using dilute acid (5% HNO_3) Cl: Protein removal using ammonium molybdate, precipitation using silver nitrate and followed by dissolution using NH_3 Cu: Acid digestion	Na: Internal standard ($^{23}Na/^{27}Al$) Cl: Exact-matching IDMS ($^{37}Cl/^{35}Cl$) Cu: Exact-matching IDMS ($^{65}Cu/^{63}Cu$) Se: Exact-matching IDMS ($^{77}Se/^{78}Se$) P: Standard addition ($^{31}P/^{73}Ge$)	Na, Cu and Se: ICP-MS Cl and P: ICP-HR-MS	Na and Cl: NIST SRM 919b Sodium chloride standard Cu: NIST SRM 3114 Copper standard solution Se: NIST SRM 3149 Selenium standard solution P: NIST SRM 3139a Phosphorus standard solution

Participating NMI/DI	Measurand	Dissolution method	Calibration method	Analytical instrument	Reference material used for calibration (traceability)
		Se: Heat-assisted digestion (HNO_3/H_2O_2) P: Microwave-assisted digestion (HNO_3/H_2O_2)			
TUBITAK UME	Na, Cl, Cu, Se, P	Na, Cu, Se and P: Microwave-assisted digestion (HNO_3/H_2O_2) Cl: Alkaline extraction (NH_4OH) – sonication and mechanical shaking	Na, Cl and P: Standard addition Cu: IDMS ($^{65}Cu/^{63}Cu$) Se: Triple IDMS ($^{78}Se/^{76}Se$)	Na, Cu and P: Thermo Element 2 SF-ICP-MS Cl and Se: Agilent 8800 QQQ-ICP-MS	Na: NIST SRM 3152 Sodium standard solution Cl: NIST SRM 919b NaCl standard Cu: IRMM 632 Se: NIST SRM 3149 Selenium standard solution, commercial isotopically enriched material

Participating NMI/DI	Measurand	Dissolution method	Calibration method	Analytical instrument	Reference material used for calibration (traceability)
					P: NIST SRM 3139a Phosphorus standard solution
LGC	Na, P	Microwave-assisted acid digestion (HNO_3/H_2O_2)	Exact single matched standard matching (ESM)	Na: ICP-OES P: ICP-QQQ-MS	Na: NIST SRM 3152a P: NIST SRM 3139a
LATU	Na, Cu, Se, P	Microwave-assisted digestion (HNO_3)	Na: Standard addition Cu: Exact-matching IDMS ($^{63}Cu/^{65}Cu$) Se: Exact-matching IDMS ($^{78}Se/^{77}Se$) P: Standard addition with internal standard ($^{31}P/^{32}S$)	Na: ICP-OES Cu, Se and P: ICP-SFMS	Na: NIST SRM 3152a Sodium standard solution Cu: SMU B12 Copper monoelemental aqueous solution Se: NIST SRM 3149 Selenium standard solution P: NIST 3139 a Phosphorus standard solution
NIST	Cl, Cu, P	Cl: Coulometric titration	Cl: Primary voltage and resistance calibration	Cl: Chloridometer	Cl: Voltage and resistance standard

Participating NMI/DI	Measurand	Dissolution method	Calibration method	Analytical instrument	Reference material used for calibration (traceability)
		Cu and P: Microwave-assisted digestion (HNO_3)	Cu: IDMS ($^{65}Cu/^{63}Cu$) P: Standard addition (^{31}P)	Cu and P: Element XR ICP-MS	Cu: SRM 3114 Copper standard solution (Lot # 121207) P: SRM 3139a Phosphorus standard solution (Lot # 060717)

5. Results and Discussion

5.1. General

Tables 6 to 10 summarise the reported results for sodium, chloride, copper, selenium and phosphorus, respectively.

Table 6. Reported results for sodium

Participating NMI/DI	Reported mass fraction (mg/kg)	Reported standard uncertainty (mg/kg)	Coverage factor, k (95 % level of confidence)	Expanded uncertainty (mg/kg)	Analytical instrument / method
NIM	3336	27	2.0	54	Flame AAS / External calibration
LNE	3239	68	2	136	ICP-HR-MS / External calibration
PTB	3352.2	8.1	2.03	17	IC / Exact matching IC
GLHK	3370	82.5	2	165	ICP-OES / Standard addition
KRISS	3395	21	1.96	41	ICP-OES / Exact matrix matching
INM	3283	24	2	48	ICP-MS / External calibration
HSA	3357	34	2	69	ICP-MS / Exact matching

Participating NMI/DI	Reported mass fraction (mg/kg)	Reported standard uncertainty (mg/kg)	Coverage factor, k (95 % level of confidence)	Expanded uncertainty (mg/kg)	Analytical instrument / method
TUBITAK UME	3321	30	2	60	ICP-HR-MS / Standard addition
LGC	3376	17	2	34	ICP-OES / Exact matching
LATU	3339	26	2	52	ICP-OES / Standard addition

Table 7. Reported results for chloride

Participating NMI/DI	Reported mass fraction (mg/kg)	Reported standard uncertainty (mg/kg)	Coverage factor, k (95 % level of confidence)	Expanded uncertainty (mg/kg)	Analytical instrument / method
NIM	3819	20	2.0	40	IC / External calibration
LNE	3743	60	2	120	ICP-HR-MS / External calibration
PTB	3878	21	2.0	42	Titrator / Exact matching argentometric titration
KRISS	3828	62	1.96	122	ICP-HR-MS / IDMS
INM	3900	50	2	100	ICP-MS / External calibration
HSA	3864	23	2	46	ICP-HR-MS / IDMS
TUBITAK UME	3908	65	2	129	QQQ-ICP-MS / Standard addition
NIST	3893.8	3.99	2.365	9.4	Chloridometer / Primary voltage and resistance calibration

Table 8. Reported results for copper

Participating NMI/DI	Reported mass fraction (mg/kg)	Reported standard uncertainty (mg/kg)	Coverage factor, k (95 % level of confidence)	Expanded uncertainty (mg/kg)	Analytical instrument / method
NMIA	1.155	0.020	2.09	0.042	ICP-HR-MS / IDMS
BIM	1.20	0.025	2	0.05	ICP-MS / External calibration
NIM	1.086	0.017	2.0	0.034	ICP-MS / IDMS
PTB	1.139	0.012	2.32	0.028	ICP-HR-MS / IDMS
GLHK	1.16	0.045	2	0.09	ICP-OES and ICP-MS / Standard addition
KRISS	1.151	0.012	1.96	0.023	ICP-HR-MS / IDMS
INM	1.10	0.05	2	0.10	ICP-MS / External calibration
HSA	1.148	0.018	2	0.036	ICP-MS / IDMS
TUBITAK UME	1.167	0.013	2	0.026	ICP-HR-MS / IDMS
LATU	1.154	0.011	2	0.022	ICP-HR-MS / IDMS
NIST	1.125	0.018	2.08	0.038	ICP-HR-MS / IDMS

Table 9. Reported results for selenium

Participating NMI/DI	Reported mass fraction (mg/kg)	Reported standard uncertainty (mg/kg)	Coverage factor, k (95 % level of confidence)	Expanded uncertainty (mg/kg)	Analytical instrument / method
NMIA	0.130	0.005	2.09	0.010	QQQ-ICP-MS / IDMS
KRISS	0.1284	0.0026	1.96	0.0052	QQQ-ICP-MS / IDMS
INM	0.125	0.006	2	0.012	ICP-MS / External calibration
HSA	0.1282	0.0025	2	0.0049	ICP-HR-MS / IDMS
TUBITAK UME	0.1302	0.0010	2	0.0019	QQQ-ICP-MS / Triple IDMS
LATU	0.1299	0.0035	2	0.0070	ICP-HR-MS / IDMS

Table 10. Reported results for phosphorus

Participating NMI/DI	Reported mass fraction (mg/kg)	Reported standard uncertainty (mg/kg)	Coverage factor, k (95 % level of confidence)	Expanded uncertainty (mg/kg)	Analytical instrument / method
NIM	129.4	1.1	2.0	2.2	ICP-OES / External calibration
KRISS	124.7	0.9	2.01	1.8	ICP-OES / Exact matrix matching
INM	126	3	2	6	ICP-MS / External calibration
HSA	125.7	3.3	2	6.6	ICP-HR-MS / Standard addition
TUBITAK UME	124.2	1.6	2	3.2	ICP-HR-MS / Standard addition
LGC	126.2	2.3	2	4.6	QQQ-ICP-MS / Exact matching
LATU	125.5	1.6	2	3.1	ICP-HR-MS / Standard addition
NIST	108.1	1.3	2.0	2.6	ICP-HR-MS / Standard addition

5.2. Calculation of the Reference Mass Fraction Values and Associated Uncertainties

In order to establish the degree of equivalence (DoE) of the measurement results submitted by the participating NMIs/DIs, a key comparison reference value (KCRV) was calculated for each measurand as a consensus value of the reported results.

On 18 April 2017, HSA drafted and circulated the Preliminary Report to the participating NMIs/DIs. The participating NMIs/DIs were requested to review the Preliminary Report and inform HSA if they identify any issues.

The reported results, consensus values and the dispersion of the reported results were presented at the CCQM IAWG Meeting (24-25 April 2017). It was highlighted that NIST's reported result for phosphorus was significantly lower than the majority of the results. After further investigation by NIST, it was concluded that the low value was caused by either poor recovery during the sample preparation process or calibration issue during the application of the standard additions method. Hence, NIST's reported result for phosphorus was excluded from the KCRV and DoE calculations.

The consensus value and the dispersion of the reported results for each analyte are summarised in Tables 11 and 12. The calculations were based on the results listed on Tables 6-10. The standard uncertainties in Table 11 were calculated using Equation 2. The MADe values were calculated by multiplying median absolute deviation (MAD) values with 1.483. The MAD values were calculated using Equation 3. The standard uncertainties in Table 12 were calculated using Equation 4.

$$Standard\ uncertainty\ = \frac{Standard\ deviation}{\sqrt{n}} \tag{2}$$

$$MAD\ = median\left(|x_i - x^*|_{i-1,2,\ldots,n}\right) \tag{3}$$

$$Standard\ uncertainty\ = 1.25 \times \frac{MADe}{\sqrt{n}} \tag{4}$$

where:

n = the number of participating institutes' results included in the calculation

x_i = the participating institute's result (mg/kg)

x^* = the median (mg/kg)

Table 11. Consensus values and the dispersions of reported results by using arithmetic mean and standard deviation

Measurand	Arithmetic mean (mg/kg)	Standard deviation (mg/kg)	n	Standard uncertainty (mg/kg)
Na	3337	46	10	15
Cl	3854	55	8	20
Cu	1.1441	0.0315	11	0.0095
Se	0.12862	0.00197	6	0.00080
P	125.96	1.68	7	0.63

Table 12. Consensus values and the dispersions of reported results by using median and median absolute deviation multiplied by 1.483 (MADe)

Measurand	Median (mg/kg)	MADe (mg/kg)	n	Standard uncertainty (mg/kg)
Na	3346	36	10	14
Cl	3871	49	8	22
Cu	1.1510	0.0178	11	0.0067
Se	0.12915	0.00133	6	0.00068
P	125.70	0.74	7	0.35

For all the measurands, good agreement was observed between the arithmetic mean and the median. Hence, as agreed at the CCQM IAWG Meeting, the median was used as an estimator of the KCRV since it is a simple and robust estimator. MADe was used for estimation of the standard uncertainty [u(KCRV)]. The u(KCRV) derived from MADe was calculated using Equation 4. The key comparison expanded uncertainty [U(KCRV)] was calculated using Equation 5 in accordance with the CCQM Guidance Note [2]. The calculated KCRV, u(KCRV) and U(KCRV) are presented in Table 13.

$$U(\mathrm{KCRV}) = 2 \times u(\mathrm{KCRV}) \quad (5)$$

Table 13. Calculated KCRV, *u*(KCRV), *U*(KCRV) and relative *U*(KCRV)

Measurand	**KCRV (mg/kg)**	***u*(KCRV) (mg/kg)**	***U*(KCRV) (mg/kg)**	**Relative *U*(KCRV) (%)**
Na	3346	14	29	0.87%
Cl	3871	22	43	1.1%
Cu	1.151	0.007	0.013	1.1%
Se	0.1292	0.0007	0.0014	1.1%
P	125.70	0.35	0.70	0.56%

The reported results together with the respective KCRV and *u*(KCRV) are presented in Figures 3-7.

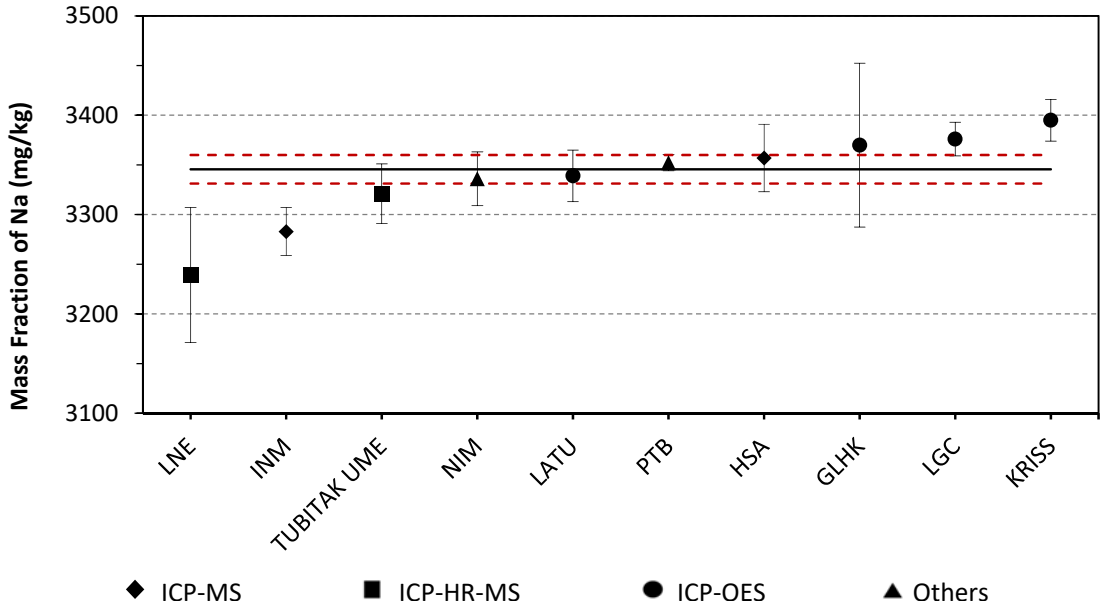

Figure 3. Results for sodium. The solid horizontal line is the KCRV and the dashed lines are the standard uncertainty of the KCRV, *u*(KCRV). Each bullet represents the reported result from the participating NMI/DI with the error bar line representing its reported standard uncertainty.

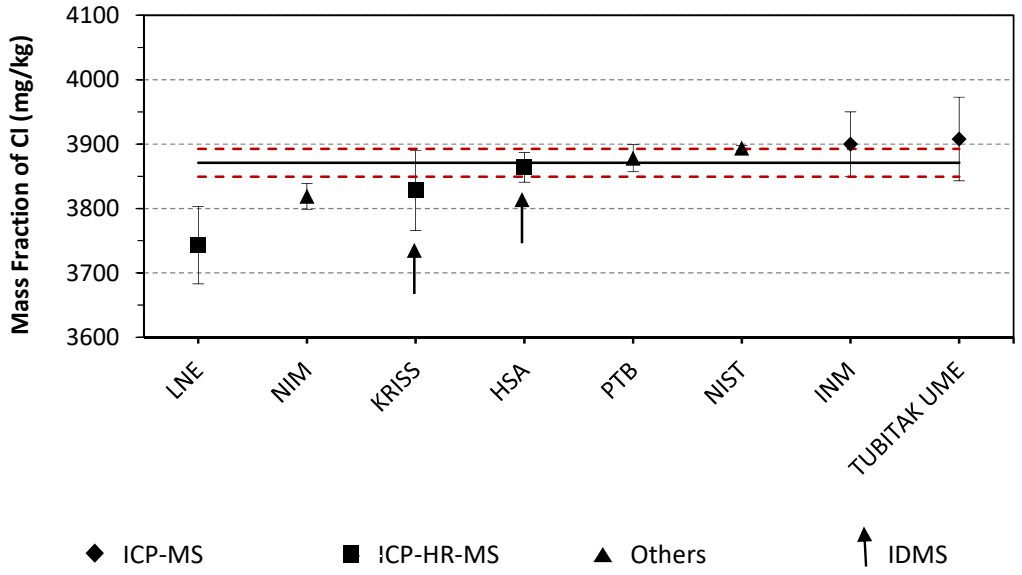

Figure 4. Results for chloride. The solid horizontal line is the KCRV and the dashed lines are the standard uncertainty of the KCRV, *u*(KCRV). Each bullet represents the reported result from the participating NMI/DI with the error bar line representing its reported standard uncertainty.

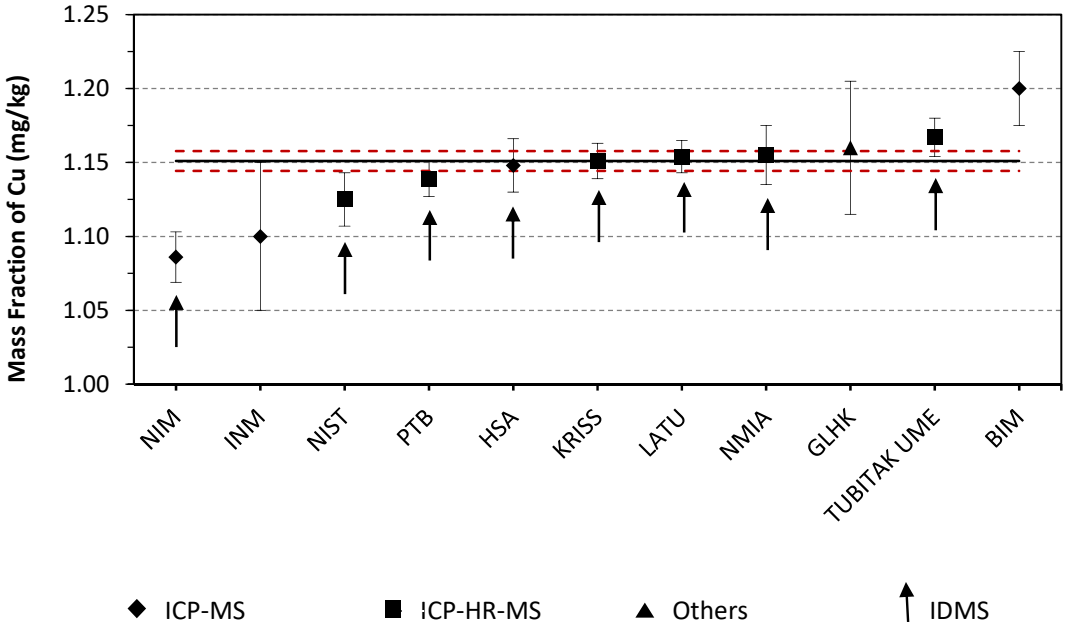

Figure 5. Results for copper. The solid horizontal line is the KCRV and the dashed lines are the standard uncertainty of the KCRV, *u*(KCRV). Each bullet represents the reported result from the participating NMI/DI with the error bar line representing its reported standard uncertainty.

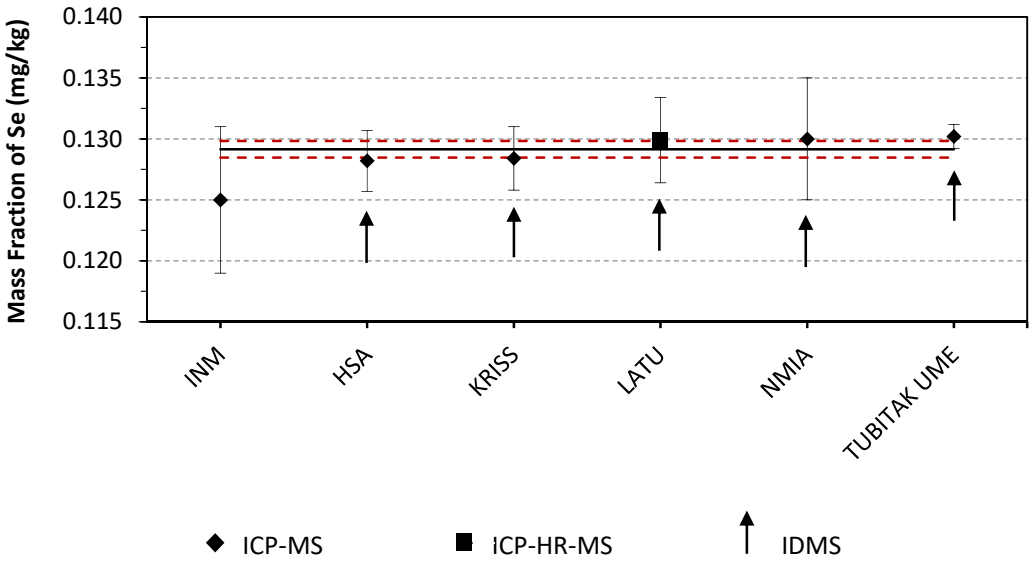

Figure 6. Results for selenium. The solid horizontal line is the KCRV and the dashed lines are the standard uncertainty of the KCRV, *u*(KCRV). Each bullet represents the reported result from the participating NMI/DI with the error bar line representing its reported standard uncertainty.

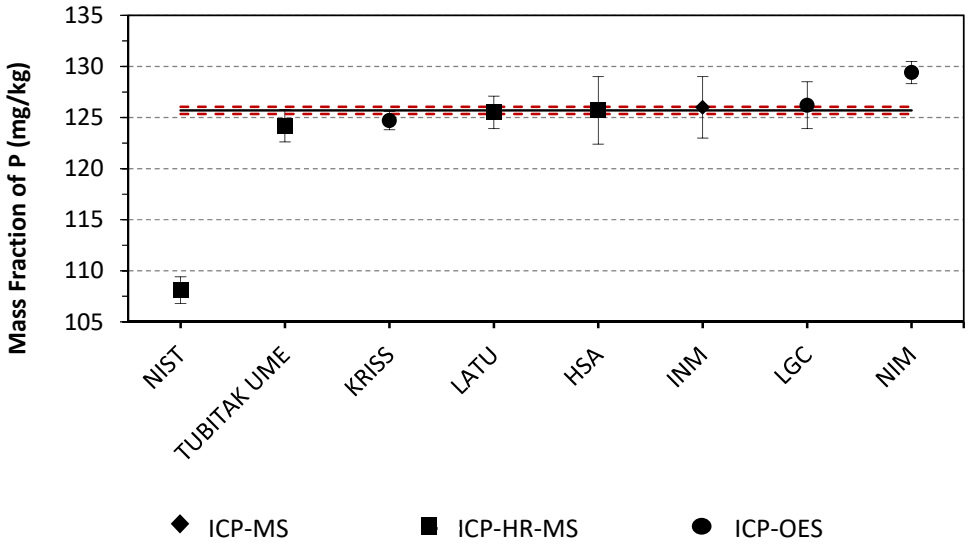

Figure 7. Results for phosphorus. The solid horizontal line is the KCRV and the dashed lines are the standard uncertainty of the KCRV, *u*(KCRV). Each bullet represents the reported result from the participating NMI/DI with the error bar line representing its reported standard uncertainty. The result submitted by NIST is not included in the calculation of KCRV.

5.3. Equivalence Statements

The degree of equivalence (DoE) and its uncertainty based on the reported measurement results with respect to the KCRV were calculated using Equations 6 and 7, respectively.

$$d_i = (x_i - \mathrm{KCRV}) \quad (6)$$

$$U(d_i) = 2 \cdot \sqrt{u(x_i)^2 + u(\mathrm{KCRV})^2} \quad (7)$$

where:

x_i = the reported result from the i^{th} participating institute (i = 1 to n)

d_i = the difference between the reported result and the KCRV

$U(d_i)$ = the expanded uncertainty (k = 2) of the difference d_i at a 95 % level of confidence

The equivalence statements for CCQM-K139 based on the KCRV are presented in Tables 14-18 and also shown in Figures 8-12.

Table 14. Equivalence statement for sodium based on the use of median as the robust estimation of KCRV

Participating NMI/DI	**Reported mass fraction, x_i (mg/kg)**	**Reported standard uncertainty, $u(x_i)$ (mg/kg)**	**Difference from KCRV, d_i (mg/kg)**	**Expanded uncertainty of the difference, $U(d_i)$ (mg/kg)**	$\frac{d_i}{U(d_i)}$	**d_i relative value (%)**	**$U(d_i)$ relative value (%)**
LNE	3239	68	-106.6	139.8	-0.76	-3.19	4.2
INM	3283	24	-62.6	58.0	-1.08	-1.87	1.7
TUBITAK UME	3321	30	-24.6	68.2	-0.36	-0.74	2.0
NIM	3336	27	-9.6	63.0	-0.15	-0.29	1.9
LATU	3339	26	-6.6	61.3	-0.11	-0.20	1.8
PTB	3352.2	8.1	6.6	36.4	0.18	0.20	1.1
HSA	3357	34	11.4	75.4	0.15	0.34	2.3
GLHK	3370	82.5	24.4	168.2	0.15	0.73	5.0

Participating NMI/DI	Reported mass fraction, x_i (mg/kg)	Reported standard uncertainty, $u(x_i)$ (mg/kg)	Difference from KCRV, d_i (mg/kg)	Expanded uncertainty of the difference, $U(d_i)$ (mg/kg)	$\frac{d_i}{U(d_i)}$	d_i relative value (%)	$U(d_i)$ relative value (%)
LGC	3376	17	30.4	47.0	0.65	0.91	1.4
KRISS	3395	21	49.4	52.4	0.94	1.48	1.6

Table 15. Equivalence statement for chloride based on the use of median as the robust estimation of KCRV

Participating NMI/DI	Reported mass fraction, x_i (mg/kg)	Reported standard uncertainty, $u(x_i)$ (mg/kg)	Difference from KCRV, d_i (mg/kg)	Expanded uncertainty of the difference, $U(d_i)$ (mg/kg)	$\frac{d_i}{U(d_i)}$	d_i relative value (%)	$U(d_i)$ relative value (%)
LNE	3743	60	-128.0	130.4	-0.98	-3.31	3.4
NIM	3819	20	-52.0	64.9	-0.80	-1.34	1.7
KRISS	3828	62	-43.0	131.8	-0.33	-1.11	3.4
HSA	3864	23	-7.0	68.8	-0.10	-0.18	1.8
PTB	3878	21	7.0	66.2	0.11	0.18	1.7
NIST	3893.8	3.99	22.8	52.0	0.44	0.59	1.3
INM	3900	50	29.0	112.3	0.26	0.75	2.9
TUBITAK UME	3908	65	37.0	139.7	0.26	0.96	3.6

Table 16. Equivalence statement for copper based on the use of median as the robust estimation of KCRV

Participating NMI/DI	**Reported mass fraction, x_i (mg/kg)**	**Reported standard uncertainty, $u(x_i)$ (mg/kg)**	**Difference from KCRV, d_i (mg/kg)**	**Expanded uncertainty of the difference, $U(d_i)$ (mg/kg)**	$\frac{d_i}{U(d_i)}$	**d_i relative value (%)**	**$U(d_i)$ relative value (%)**
NIM	1.086	0.017	-0.065	0.037	-1.75	-5.65	3.2
INM	1.10	0.05	-0.051	0.101	-0.50	-4.43	8.8
NIST	1.125	0.018	-0.026	0.040	-0.64	-2.26	3.5
PTB	1.139	0.012	-0.012	0.032	-0.38	-1.04	2.8
HSA	1.148	0.018	-0.003	0.039	-0.08	-0.26	3.4
KRISS	1.151	0.012	0.000	0.028	0.00	0.00	2.4
LATU	1.154	0.011	0.003	0.027	0.11	0.26	2.3
NMIA	1.155	0.020	0.004	0.044	0.09	0.35	3.9
GLHK	1.16	0.045	0.009	0.091	0.10	0.78	7.9
TUBITAK UME	1.167	0.013	0.016	0.030	0.53	1.39	2.6
BIM	1.20	0.025	0.049	0.052	0.94	4.26	4.5

Table 17. Equivalence statement for selenium based on the use of median as the robust estimation of KCRV

Participating NMI/DI	Reported mass fraction, x_i (mg/kg)	Reported standard uncertainty, $u(x_i)$ (mg/kg)	Difference from KCRV, d_i (mg/kg)	Expanded uncertainty of the difference, $U(d_i)$ (mg/kg)	$\frac{d_i}{U(d_i)}$	d_i relative value (%)	$U(d_i)$ relative value (%)
INM	0.125	0.006	-0.0042	0.0121	-0.34	-3.21	9.4
HSA	0.1282	0.0025	-0.0010	0.0053	-0.18	-0.74	4.1
KRISS	0.1284	0.0026	-0.0008	0.0054	-0.14	-0.58	4.4
LATU	0.1299	0.0035	0.0008	0.0072	0.10	0.58	5.6
NMIA	0.130	0.005	0.0009	0.0106	0.08	0.66	8.2
TUBITAK UME	0.1302	0.0010	0.0011	0.0027	0.40	0.81	2.1

Table 18. Equivalence statement for phosphorus based on the use of median as the robust estimation of KCRV

Participating NMI/DI	Reported mass fraction, x_i (mg/kg)	Reported standard uncertainty, $u(x_i)$ (mg/kg)	Difference from KCRV, d_i (mg/kg)	Expanded uncertainty of the difference, $U(d_i)$ (mg/kg)	$\frac{d_i}{U(d_i)}$	d_i relative value (%)	$U(d_i)$ relative value (%)
NIST	108.1	1.3	-17.6	2.7	-6.43	-14.00	2.2
TUBITAK UME	124.2	1.6	-1.5	3.3	-0.45	-1.19	2.6
KRISS	124.7	0.9	-1.0	2.0	-0.50	-0.80	1.6
LATU	125.5	1.6	-0.2	3.3	-0.06	-0.16	2.6
HSA	125.7	3.3	0.0	6.7	0.00	0.00	5.3
INM	126	3	0.3	6.1	0.05	0.24	4.8
LGC	126.2	2.3	0.5	4.7	0.11	0.40	3.7
NIM	129.4	1.1	3.7	2.4	1.57	2.94	1.9

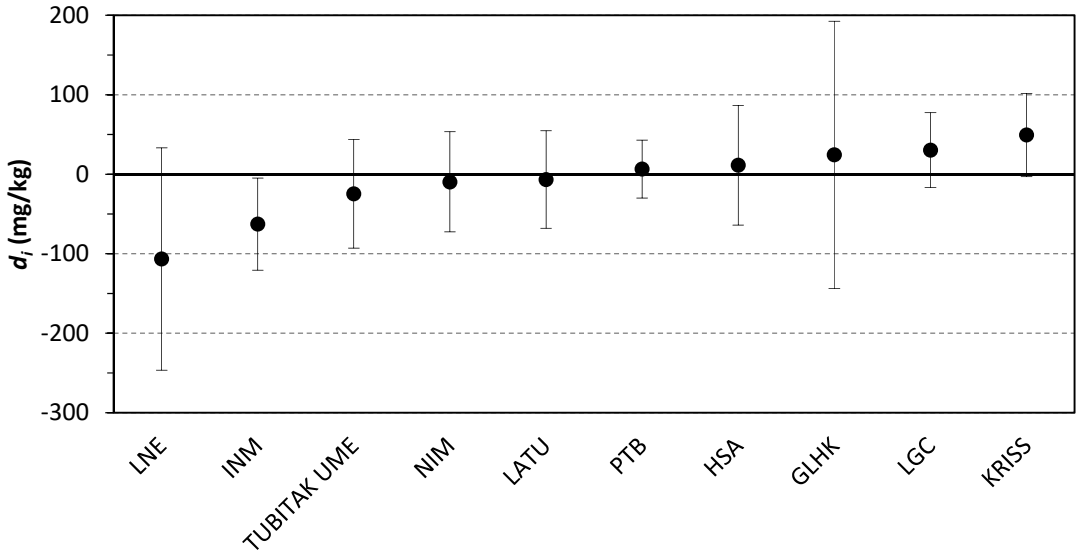

Figure 8. Equivalence statement for sodium based on the use of median as the robust estimation of KCRV. Each error bar line represents the expanded uncertainty.

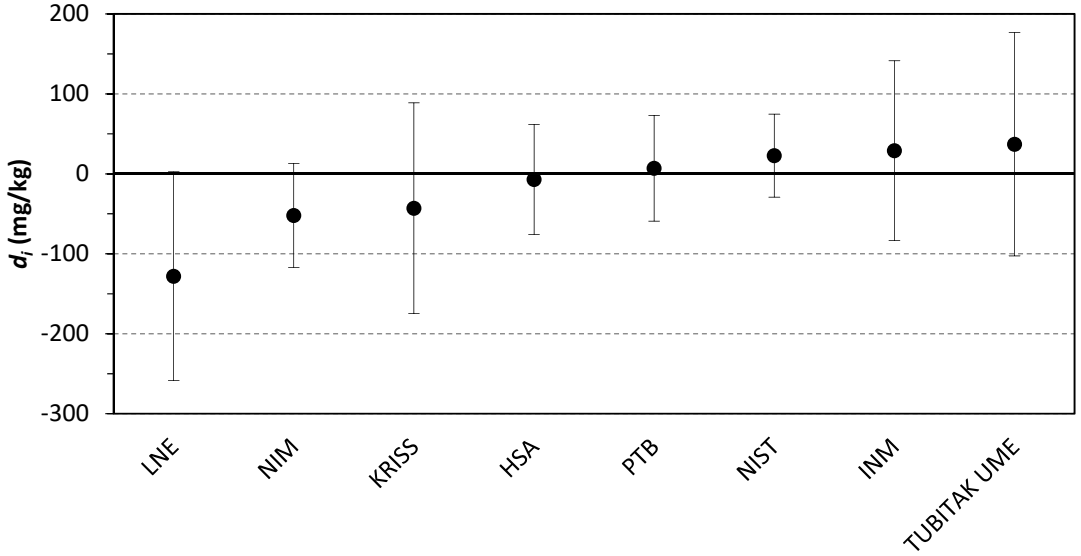

Figure 9. Equivalence statement for chloride based on the use of median as the robust estimation of KCRV. Each error bar line represents the expanded uncertainty.

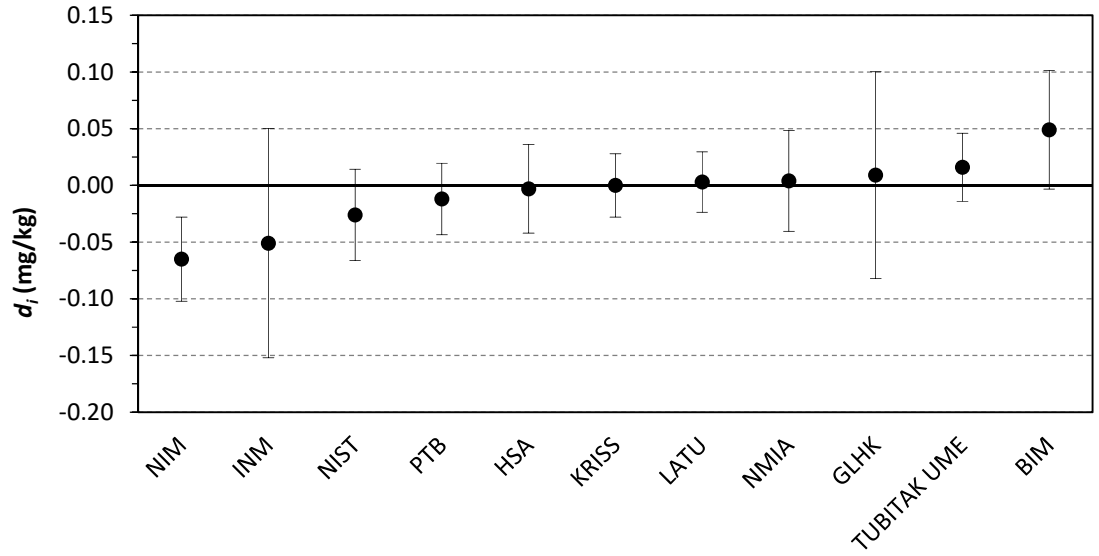

Figure 10. Equivalence statement for copper based on the use of median as the robust estimation of KCRV. Each error bar line represents the expanded uncertainty.

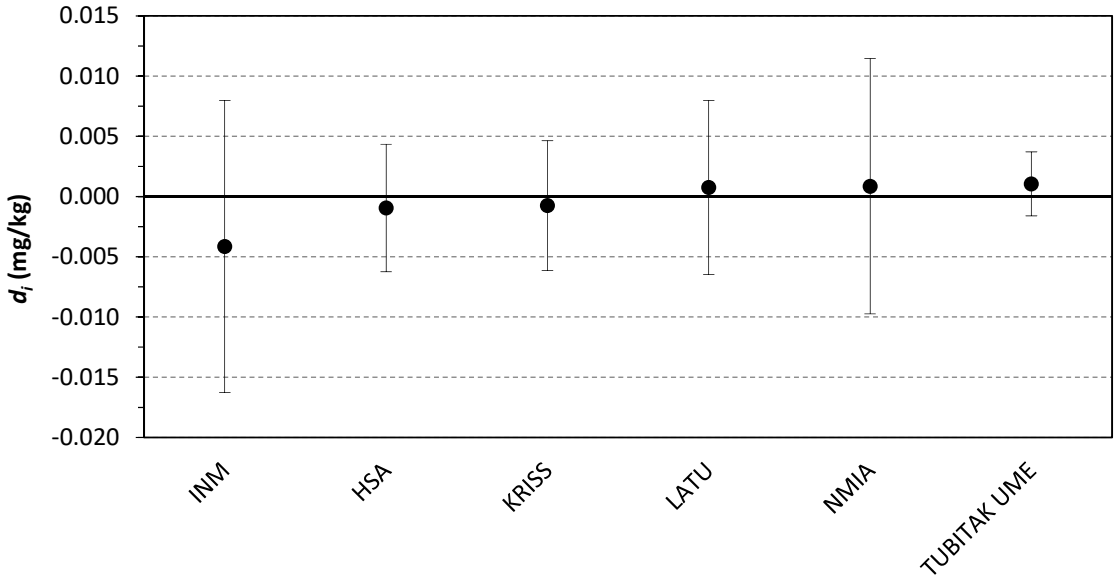

Figure 11. Equivalence statement for selenium based on the use of median as the robust estimation of KCRV. Each error bar line represents the expanded uncertainty.

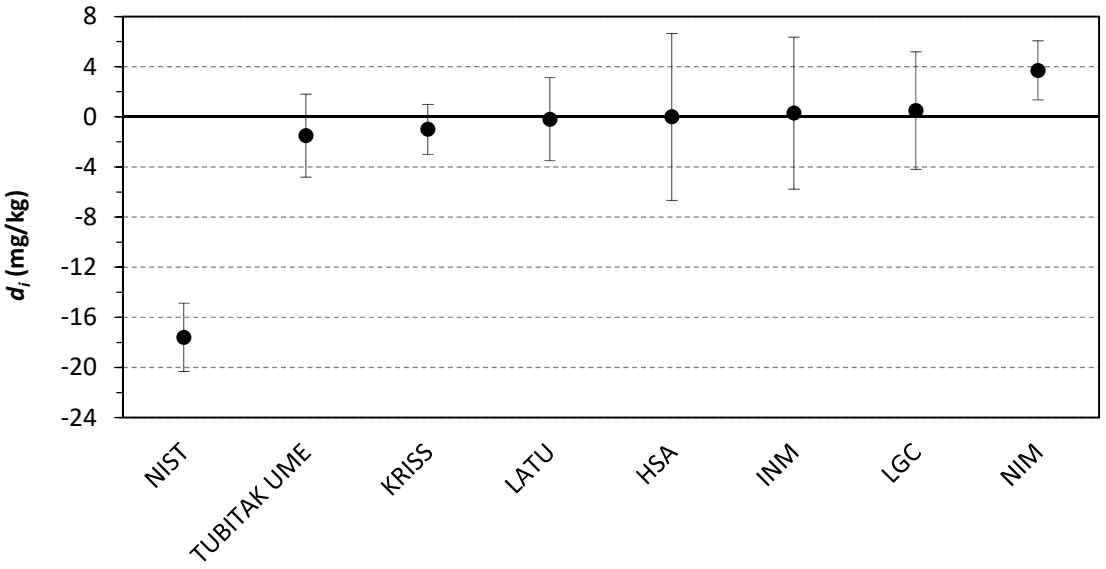

Figure 12. Equivalence statement for phosphorus based on the use of median as the robust estimation of KCRV. Each error bar line represents the expanded uncertainty. The result submitted by NIST is not included in the calculation of KCRV.

6. Demonstration of Core Capabilities

All NMIs/DIs participating in CCQM-K139 submitted their Inorganic Core Capabilities (CCs) Tables to HSA. The Tables are summarised in the Appendix. This approach is used to improve the efficiency and effectiveness of key and/or supplementary comparisons in supporting CMC claims. New CMC claims can be supported by describing the capabilities required to deliver the measurement service claimed and by referencing the core capabilities that are successfully demonstrated through participation in the key comparison.

7. Conclusion

For the analysis of sodium, copper, selenium and phosphorus, most of the participating NMIs/DIs employed microwave-assisted digestion and acid digestion (with or without heating) sample dissolution. For the analysis of chloride, in addition to the microwave-assisted digestion and acid digestion, other techniques were employed. These included matrix separation, alkaline extraction and coulometric titration. For sodium and phosphorus, ICP-MS and ICP-OES were the two most commonly used instrumental techniques. Other techniques used included IC and FAAS. For chloride, copper and selenium, the most widely used instrumental technique was ICP-MS. Other techniques used included IC, titration, micro-coulometry and ICP-OES.

For all measurands, most participating institutes' results were found to be consistent according to their equivalence statements. All the participating institutes obtained values of $d_i/U(d_i)$ within ± 1 for chloride and selenium. For sodium and copper, with the exception of one institute, other NMIs/DIs obtained values of $d_i/U(d_i)$ within ± 1. For phosphorus, most NMIs/DIs obtained values of $d_i/U(d_i)$ within ± 1, except for two institutes.

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NMI/DI (Country)	Contact person(s) and/or analyst(s)
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BIM (Bulgaria)	Veronika Ivanova
NIM (P. R. China)	Liuxing Feng, Jun Wang, Naijie Shi, Haifeng Li, Yanjie Cui
LNE (France)	M. Estela del Castillo Busto, Paola Fisicaro
PTB (Germany)	Carola Pape, Jessica Towara, Silvia Ulbrich, Reinhard Jaehrling, Olaf Rienitz
GLHK (Hong Kong SAR, China)	Wai-hong Fung, Michael Ho-pan Yau
KRISS (Korea)	Yong-Hyeon Yim, Kyoung-Seok Lee, Sung Woo Heo, Myung Sub Han, Youngran Lim, Hyung Sik Min
INM (Romania)	Mirella Buzoianu
TUBITAK UME (Turkey)	Suleyman Z. Can, Betul Ari, Oktay Cankur
LGC (UK)	Heidi Goenaga Infante, Christian Deitrich, Sarah Hill
LATU (Uruguay)	Ramiro Pérez-Zambra, Romina Napoli, Elizabeth Ferreira
NIST (USA)	Stephen Long, W. Clay Davis, Regina Easley

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References

1. International Standard Organisation, ISO Guide 35: Reference materials – General and statistical principles for certification, Geneva, Switzerland, 2006.
2. CCQM Guidance Note: Estimation of consensus KCRV and associated degrees of equivalence, Version 10, 2013.

Appendix

Inorganic Core Capabilities

Summary Table

CCQM Study : CCQM-K139 Elements in Human Serum

Institute(s) : NMIA (Cu, Se), NIM (Cu), PTB (Cu), KRISS (Cl, Cu, Se), HSA (Cl, Cu, Se), TUBITAK UME (Cu, Se), LATU (Cu, Se), NIST (Cu)

Method : ID-ICP-MS

Analyte(s) : Cl, Cu, Se

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Contamination control and correction *All techniques and procedures employed to reduce potential contamination of samples as well as blank correction procedures. The level of difficulty is greatest for analytes that are environmentally ubiquitous and also present at very low concentrations in the sample.*		NMIA, NIM, PTB, KRISS, HSA, TUBITAK UME, LATU, NIST	NMIA: None. Only minor backgrounds were observed during this project. TUBITAK UME: In order to minimize the possible contamination of sample, ultrapure reagents and pre-cleaned unused labwares were used during the analysis. LATU: Samples and calibrants were prepared using high purity nitric acid (in-house sub-boiling distilled) in an ISO 14644-1 Class 6 cleanroom to avoid contamination. NIST: Cu background minimal ~ 900 CPS, no carryover for repeat measurements using interspersed blanks.
Digestion/dissolution of organic matrices *All techniques and procedures used to bring a sample that is primarily organic in nature into solution*		NMIA, NIM, PTB, KRISS, HSA,	NMIA: None. Microwave digestions were performed easily. TUBITAK UME: Closed vessel microwave assisted

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
suitable for liquid sample introduction to the ICP.		TUBITAKUME, LATU, NIST	sample digestion was used to decompose the sample matrix, and to bring the analyte into solution. LATU: Samples, calibrants and quality control CRMs were spiked and digested with nitric acid in a closed vessel microwave digestion system. NIST: Closed vessel microwave digestion using nitric acid.
Digestion/dissolution of inorganic matrices *All techniques and procedures used to bring a sample that is primarily inorganic in nature into solution suitable for liquid sample introduction to the ICP.*	NMIA, PTB, HSA, TUBITAKUME, LATU, NIST	KRISS	NMIA: N/A.
Volatile element containment *All techniques and procedures used to prevent the loss of potentially volatile analyte elements during sample treatment and storage.*	NMIA, PTB, KRISS, HSA, TUBITAKUME, LATU, NIST		NMIA: N/A.
Pre-concentration *Techniques and procedures used to increase the concentration of the analyte introduced to the ICP. Includes evaporation, ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*	NMIA, PTB, KRISS, HSA (Cu, Se), LATU, NIST	HSA (Cl), TUBITAKUME	NMIA: N/A. HSA: Chloride was precipitated using silver nitrate. TUBITAK UME: For Se, the solvent evaporation to dryness followed by dissolution in dilute nitric acid was performed before the measurements.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Vapor generation *Techniques such as hydride generation and cold vapor generation used to remove the analyte from the sample as a gas for introduction into the ICP.*	NMIA, PTB, KRISS, HSA, TUBITAKUME, LATU, NIST		NMIA: N/A.
Matrix separation *Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction, precipitation procedures, but not vapor generation procedures. Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*	NMIA, PTB, KRISS, HSA (Cu, Se), TUBITAKUME, LATU, NIST	HSA (Cl)	NMIA: N/A. HSA: Chloride was precipitated using silver nitrate.
Spike equilibration with sample *The mixing and equilibration of the enriched isotopic spike with the sample.*		NMIA, NIM, PTB, KRISS, HSA, TUBITAKUME, LATU, NIST	NMIA: Spiked prior to closed vessel microwave digestion, equilibration assumed during the microwave stage. TUBITAK UME: Measurements of blend solutions were performed at least one day after preparation for isotopic equilibration. NIST: Closed vessel microwave digestion using nitric acid.
Signal detection *The detection and recording of the analyte isotope signals. The degree of difficulty increases for analytes*	NMIA (Cu), PTB, HSA (Cl, Cu),	NMIA (Se), KRISS, HSA (Se),	NMIA: Low counts for Se. HSA: Blends were diluted with 3% methanol to enhance

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
present at low concentrations, of low isotopic abundance, or that are poorly ionized.	TUBITAK UME	LATU, NIST	the signal detection for selenium. LATU: Se measurements were performed at high resolution (R≈10000) causing poor sensitivity, decreasing precision.
Memory effect *Any techniques used to avoid, remove or reduce the carry-over of analyte between consecutively measured standards and/or samples.*	PTB, HSA	NMIA, KRISS, TUBITAK UME, LATU, NIST	NMIA: None. No problematic memory effects observed. TUBITAK UME: The lines were thoroughly rinsed to get rid of any memory effects between the samples and standards. Background measurements were performed before each measurement. NIST: Process blanks interspersed periodically between blocks of samples and controls; count rates monitored for repeatedly run blanks indicated no cross contamination.
Correction or removal of isobaric/polyatomic interferences *Any techniques used to remove, reduce, or mathematically correct for interferences caused by mass overlap of analyte isotopes with isobaric or polyatomic species. Includes collision cell techniques, high resolution mass spectrometry, or chemical separations. The relative concentrations and sensitivities of the analyte isotopes and the interfering species will affect the degree of difficulty.*		NMIA, PTB, KRISS, HSA, TUBITAK UME, LATU, NIST	NMIA: On the ICP-SF-MS minimum of medium resolution required for Cu and high resolution for Se measurement. On the ICP-MS-Q-MS reaction gases such as O_2 and H_2 required for Se and reaction gas such as O_2 or a collision gas such as He required for Cu. PTB: Removal of NaAr (63 g/mol) interference requires the use of high resolution during the ICP-MS measurements.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
			KRISS: For Cl, high resolution was used to remove isobaric/polyatomic interferences. For Cu, medium resolution was used to remove isobaric/polyatomic interferences. For Se, oxygen reaction of Se^+ to SeO^+ in the collision cell of ICP-QQQMS was used to remove isobaric/polyatomic interferences. TUBITAK UME: For Se, measurements were performed using H_2 reaction gas at QQQ-ICP-MS instrument to avoid possible isobaric interferences. LATU: For Cu, medium resolution (R>4000) was used to resolve interferences. For Se, high resolution (R≈10000) was used to resolve interferences. NIST: Sector-field ICP-MS with a resolution > 4400 at *m/z* 115 (In) tested using a 1 ng/g tune solution. This resolution is adequate to resolve all polyatomic and isobaric interferences.
Detector deadtime correction *Measurement of, and correction for, ion detector deadtime. Importance increases in situations where high ion count rates are encountered.*	NMIA, PTB	KRISS, HSA, TUBITAK UME, LATU, NIST	HSA: Sample and calibration blends intensities were matched to reduce the significance of this effect. TUBITAK UME: Detector dead time was measured before measurements.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
			NIST: 28 nS; minimal effect due to measured count rates.
Mass bias/fractionation control and correction *Techniques used to determine, monitor, and correct for mass bias/fractionation.*	NMIA	NIM, PTB, KRISS, HSA, TUBITAK UME, LATU, NIST	HSA: Sample and calibration blends were bracketed with a standard solution with known isotopic composition to correct for mass bias. TUBITAK UME: For Cu, mass bias correction factors were determined between runs and included in the calculations. NIST: Mass bias sample (SRM 3114) interspersed periodically between blocks of samples and controls.
Spike calibration *Techniques used to determine the analyte concentration in the enriched isotopic spike solution.*	NMIA	NIM, PTB, KRISS, HSA, TUBITAK UME, LATU, NIST	HSA: Exact-matching IDMS was used TUBITAK UME: Triple IDMS method was applied for Se using commercial isotopically enriched spike material. LATU: Exact matching IDMS. NIST: Reverse ID spike calibration using SRM 3114.

Inorganic Core Capabilities

Summary Table

CCQM Study : CCQM-K139 Elements in Human Serum

Institute(s) : BIM (Cu), LNE (Na, Cl), GLHK (Cu), INM (Na, Cl, Cu, Se, P), HSA (Na, P), TUBITAK UME (Na, Cl, P), LGC (P), LATU (P), NIST (P)

Method : ICP-MS (without Isotope Dilution)

Analyte(s) : Na, Cl, Cu, Se and P

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Contamination control and correction *All techniques and procedures employed to reduce potential contamination of samples as well as blank correction procedures. The level of difficulty is greatest for analytes that are environmentally ubiquitous and also present at very low concentrations in the sample.*		BIM, LNE, GLHK, INM, HSA, TUBITAK UME, LGC, LATU, NIST	BIM: Blanks taken into account. Ultrapure water and suprapur nitric acid were used. LNE: High purity reagents needed. INM: Blank values for low mass fraction of Se under control. Contamination control especially for Se and Cu. TUBITAK UME: In order to minimize the possible contamination of sample, ultrapure reagents and pre-cleaned unused labwares were used during the analysis. LGC: All sample preparation was performed in vials pre-soaked in 5% nitric acid and rinsed with high purity water before use. Microwave vessels were submitted to a cleaning program after/before each new sample batch. Instrument parts such as cones, spray chamber or tubing were cleaned or replaced for each new batch.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
			Subtraction of the raw blank counts (dilution & digestion) from the sample counts. LATU: Samples and calibrants were prepared using high purity nitric acid (in-house sub-boiling distilled) in an ISO 14644-1 Class 6 cleanroom to avoid contamination. NIST: P background minimal ~ 1000 CPS, no carryover for repeat measurements using interspersed blanks.
Digestion/dissolution of organic matrices *All techniques and procedures used to bring a sample that is primarily organic in nature into solution suitable for liquid sample introduction to the ICP.*	BIM	LNE, GLHK, INM, HSA, TUBITAKUME, LGC, LATU, NIST	LNE: All samples were diluted with 4 mmol/L nitric acid. INM: Dilution 1:50 with HNO_3 for Na and P. Dilution 1:50 with a mixture 1.5 % TMAH and 1.5 % HCl. Validation with SRM NIST 909b (Na and Cl), 909c (Se), ERM DA120a. TUBITAK UME: For Na and P, closed vessel microwave assisted sample digestion was used to decompose the sample matrix, and to bring the analyte into solution. For Cl, samples were heated in alkaline medium to extract the analyte. LGC: Closed vessel microwave digestion with nitric acid and hydrogen peroxide mixture. Direct dilution of the serum samples in a diluted acid matrix (0.5% nitric) caused a low recovery

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
			of P compared to the digested samples. LATU: Samples and quality control CRMs were digested with nitric acid in a closed vessel microwave digestion system. NIST: Closed vessel microwave digestion using nitric acid.
Digestion/dissolution of inorganic matrices *All techniques and procedures used to bring a sample that is primarily inorganic in nature into solution suitable for liquid sample introduction to the ICP.*	BIM, LNE, INM, HSA, TUBITAKUME, LGC, LATU, NIST	GLHK	LGC: Not applicable.
Volatile element containment *All techniques and procedures used to prevent the loss of potentially volatile analyte elements during sample treatment and storage.*	BIM, LNE, GLHK, INM, HSA, LGC, LATU, NIST	TUBITAKUME	TUBITAK UME: For Cl, leaching of the analyte was performed at low temperatures and closed containers. LGC: Not applicable.
Pre-concentration *Techniques and procedures used to increase the concentration of the analyte introduced to the ICP. Includes evaporation, ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*	BIM, LNE, GLHK, INM, HSA, TUBITAKUME, LGC, LATU, NIST		LGC: Not applicable.
Vapor generation *Techniques such as hydride generation and cold vapor*	BIM, LNE, GLHK,		LGC: Not applicable.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
generation used to remove the analyte from the sample as a gas for introduction into the ICP.	INM, HSA, TUBITAK UME, LGC, LATU, NIST		
Matrix separation *Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*	BIM, LNE, GLHK, INM, HSA, TUBITAK UME, LGC, LATU, NIST		LGC: Not applicable.
Calibration of analyte concentration *The preparation of calibration standards and the strategy for instrument calibration. Includes external calibration and standard additions procedures.*		BIM, LNE, GLHK, INM, HSA, TUBITAK UME, LGC, LATU, NIST	BIM: External calibration. LNE: Multi-point gravimetric external calibration using two independent primary calibration NaCl solutions. GLHK: Gravimetric standard addition. INM: Instrument calibration SRMs. Both external calibration and standard addition procedures. All calibration standards prepared gravimetrically. TUBITAK UME: Gravimetric standard addition method was used for the calibration. For Na and P, in order to monitor and

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
			minimize the drift on the signal, internal standard was used. LGC: Exact single matched standard matching (ESM). Preparation of a calibration blend with the same analyte concentration as the samples. An internal standard (IS) solution (Ge) is added gravimetrically to each sample and the calibration blend to obtain an analyte/IS ratio close to 1 prior to digestion. LATU: Standard addition calibration with internal standard was applied. NIST: Performed symmetrically clustered standard additions using 12 digested aliquots of serum. Six unspiked samples and six spiked samples. Used SRM 3139a P solution as spike.
Signal detection *The detection and recording of the analyte isotope signals. The degree of difficulty increases for analytes present at low concentrations, of low isotopic abundance, or that are poorly ionized.*	LNE, INM (for Na, P and Ag), HSA, TUBITAK UME, LGC	BIM, GLHK, INM (for Cu and Se), LATU, NIST	BIM: Measurement of ^{63}Cu and ^{65}Cu. Only ^{65}Cu was used for the calculations. INM: Both $^{62.9298}$Cu and $^{64.9278}$Cu isotopes measured. Both $^{77.9173}$Se and $^{81.9167}$Se measured. Due to the analyte signals $^{62.9298}$Cu and $^{77.9173}$Se isotopes selected. LGC: Using 8800 QQQ-ICP-MS technology in He MS/MS mode there was enough signal intensity for P over the background/blank.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Memory effect *Any techniques used to avoid, remove or reduce the carry-over of analyte between consecutively measured standards and/or samples.*	LNE, HSA, LGC	BIM, GLHK, INM, TUBITAK UME, LATU, NIST	BIM: Rinsing with 2% nitric acid between the runs. Blank measurement performed before each sample or standard. INM: Sequence of calibration and measurements performed in such a way to minimize memory effects. Longer washing period between successive measurements when TMAH solvent was used. TUBITAK UME: Lines were rinsed using the same solutions used for the dilution of samples during the measurements. Background measurements were performed between the samples. LGC: Rinse (5% nitric acid) after each sample. No carry over was observed between samples. NIST: Process blanks interspersed periodically between blocks of samples and controls; count rates monitored for repeatedly run blanks indicated no cross contamination.
Correction or removal of isobaric/polyatomic interferences *Any techniques used to remove, reduce, or mathematically correct for interferences caused by mass overlap of analyte isotopes with isobaric or polyatomic species. Includes collision cell techniques,*	BIM	LNE, GLHK, INM, HSA, TUBITAK UME, LGC,	LNE: All measurements were performed in high resolution ICP-MS (HR-ICP-MS). PTB: Removal of NaAr (63 g/mol) interference requires the use of high resolution during the ICPMS measurements.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
high resolution mass spectrometry, or chemical separations. The relative concentrations and sensitivities of the analyte isotopes and the interfering species will affect the degree of difficulty.		LATU, NIST	INM: In accordance with the recommendations given in the instrument manual. Rh internal standard used for Se and Cu. TUBITAK UME: HR-ICP-MS was operated at medium resolution mode for the measurements of Na and P to avoid any isobaric interferences. For Cl, mass shift function of QQQ (35 to 37 using H_2) was employed to avoid any possible interferences. LGC: A triple quadrupole ICP-MS with collision-reaction cell technology was used applying He in MS/MS mode with Q1 set to *m/z* 31 and Q2 at *m/z* 31.This setting significantly reduces interferences (NOH^+ NO^+) arising from the presence of nitric acid and the sample matrix. LATU: Medium resolution (R>4000) was used to resolve interferences. NIST: Sector-field ICP-MS with a resolution > 4400 at *m/z* 115 (In) tested using a 1 ng/g tune solution. This resolution is adequate to resolve all polyatomic and isobaric interferences.
Correction or removal of matrix-induced signal suppression or enhancement	BIM, LNE, GLHK, HSA (Na), TUBITAK	INM, HSA (P), LGC, LATU	INM: In accordance with the instrument manual recommendations.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Chemical or instrumental procedures used to avoid or correct for matrix-induced signal suppression or enhancement.	UME, NIST		HSA: Standard addition was used for phosphorus. LATU: Gravimetric standard addition with internal standard. LGC: Microwave digestion performed so all samples and the calibration standard in the same matrix. Dilution applied with matched acid concentration (5% nitric) prior to analysis.
Detector deadtime correction *Measurement of, and correction for, ion detector deadtime. Importance increases in situations where high ion count rates are encountered.*	BIM, HSA, TUBITAK UME, LGC	LNE, GLHK, INM, LATU, NIST	LNE: Calibration standards and samples measured at same intensity levels. INM: In accordance with the instrument manual recommendations. LGC: Not applicable as ESM was used. Sample and calibration blend intensities and ratios were closely matched and the detector dead time effect cancels. NIST: 28 nS; minimal effect due to measured count rates.
Mass bias/fractionation control and correction *Techniques used to determine, monitor, and correct for mass bias/fractionation.*	BIM, LNE, GLHK, HSA, TUBITAK UME, LGC, LATU, NIST	INM	INM: In accordance with the instrument procedure and use of CRMs and SRMs. In the case of indirect chloride measurement, validation with NIST SRM 909b level II applied to the entire analytical procedure. LGC: Not applicable.

Inorganic Core Capabilities

Summary Table

CCQM Study : CCQM-K139 Elements in Human Serum

Institute(s) : NIM (P), GLHK (Na, Cu), KRISS (Na, P), LGC (Na), LATU (Na)

Method : ICP-OES

Analyte(s) : Na, Cu, P

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Contamination control and correction *All techniques and procedures employed to reduce potential contamination of samples as well as blank correction procedures. The level of difficulty is greatest for analytes that are environmentally ubiquitous and also present at very low concentrations in the sample.*	LGC	NIM, GLHK, KRISS, LATU	LGC: Very high concentration of Na so no high impact of blanks, which were constant. Despite of this, appropriate pre-cleaning of microwave vessels and sample vials was undertaken. LATU: Samples and calibrants were prepared using high purity nitric acid (in-house sub-boiling distilled) in an ISO 14644-1 Class 6 cleanroom to avoid contamination.
Digestion/dissolution of organic matrices *All techniques and procedures used to bring a sample that is primarily organic in nature into solution suitable for liquid sample introduction to the ICP.*		NIM, GLHK, KRISS, LGC, LATU	LGC: Closed vessel microwave digestion with nitric acid and hydrogen peroxide mixture. Direct dilution of the serum samples in a diluted acid matrix (0.5% nitric) caused a low recovery of P compared to the digested samples. LATU: Samples and quality control CRMs were digested with nitric acid in a closed vessel microwave digestion system.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Digestion/dissolution of inorganic matrices *All techniques and procedures used to bring a sample that is primarily inorganic in nature into solution suitable for liquid sample introduction to the ICP.*	LGC, LATU	GLHK, KRISS	LGC: Not applicable.
Volatile element containment *All techniques and procedures used to prevent the loss of potentially volatile analyte elements during sample treatment and storage.*	GLHK, KRISS, LGC, LATU	NIM	LGC: Not applicable.
Pre-concentration *Techniques and procedures used to increase the concentration of the analyte introduced to the ICP. Includes evaporation, ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*	GLHK, KRISS, LGC, LATU		LGC: Not applicable.
Vapor generation *Techniques such as hydride generation and cold vapor generation used to remove the analyte from the sample as a gas for introduction into the ICP.*	GLHK, KRISS, LGC, LATU		LGC: Not applicable.
Matrix separation *Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction, precipitation procedures, but not vapor generation procedures. Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction,*	GLHK, KRISS, LGC, LATU	NIM	LGC: Not applicable.

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
precipitation procedures, but not vapor generation procedures.			
Calibration of analyte concentration *The preparation of calibration standards and the strategy for instrument calibration. Includes external calibration and standard additions procedures.*		NIM, GLHK, KRISS, LGC, LATU	GLHK: Gravimetric standard addition. KRISS: Iterative procedure is required for exact matrix matching calibration. LGC: Exact single matched standard matching (ESM). Preparation of a calibration blend with the same analyte concentration as the samples. An internal standard (IS) solution (Sc) is added gravimetrically to each sample and the calibration blend to obtain an analyte/IS ratio close to 1 prior to digestion. LATU: Standard addition calibration was applied.
Signal detection *The detection and recording of the analyte signals. The degree of difficulty increases for analytes present at low concentrations, or that are have weak emission lines.*	LGC	NIM, GLHK, KRISS, LATU	LGC: High Na concentration so no problem to detect it in digests over the blank signals. The instrument was used in SVDV mode. Several wavelengths were used and the optimal selected.
Memory effect *Any techniques used to avoid, remove or reduce the carry-over of analyte between consecutively measured standards and/or samples.*		NIM, GLHK, KRISS, LGC, LATU	LGC: 5% nitric acid rinse performed at high pump speed in between each sample analysis. No significant carry over was observed.
Complex spectral backgrounds	GLHK	NIM, KRISS,	LGC: Instrumental software applied background

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Any techniques used to remove, reduce, or mathematically correct for interferences caused by the overlap of analyte emission lines with atomic, ionic, or molecular emission from matrix components. The relative concentrations and sensitivities of the analyte and the interfering species will affect the degree of difficulty. Samples containing high concentration matrix components with large numbers of emission lines or molecular bands may increase the measurement challenge.		LGC, LATU	correction. Choice of various wavelengths selection of the optimal (highest intensities with best signal/peak shape) used for the calculations.
Correction or removal of matrix-induced signal suppression or enhancement *Chemical or instrumental procedures used to avoid or correct for matrix-induced signal suppression or enhancement. High concentrations of acids, dissolved solids, or easily ionized elements will increase the degree of difficulty.*	GLHK	NIM, KRISS, LGC, LATU	KRISS: Major matrix elements were investigated for matrix matching calibration. LGC: Microwave digestion performed so all samples and the calibration standard in the same matrix. Optimized dilution factor of digest solutions. Dilution applied with matched acid concentration (5% nitric) prior to analysis. LATU: Standard addition calibration was applied.

Inorganic Core Capabilities

Summary Table

CCQM Study : CCQM-K139 Elements in Human Serum

Institute(s) : PTB (Cl)

Method : Titration (TI)

Analyte(s) : Cl

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Contamination control and correction *All techniques and procedures employed to reduce potential contamination of samples as well as blank correction procedures. The level of difficulty is greatest for analytes that are environmentally ubiquitous and also present at very low concentrations in the sample.*	PTB		
Digestion/dissolution of organic matrices *All techniques and procedures used to bring a sample that is primarily organic in nature into solution suitable for liquid sample introduction to the ion chromatography system.*		PTB	PTB: Alkalic digestion in open vessels is the only option, but there is always the danger of poor recoveries (losses of Cl via HCl).
Calibration of analyte concentration *The preparation of calibration standards and the strategy for instrument calibration. Includes external calibration and standard addition procedures as well as the use of an internal standard.*		PTB	
Signal detection *The detection and recording of the analyte signals. The degree of*	PTB		

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
difficulty increases for analytes present at low concentrations.			
End-point detection *Procedures used to determine end-points. (e.g., high difficulty for small slopes etc.)*		PTB	
Dry mass correction *Choice and preparation/preconditioning of desiccant (drying agent), mass determination (control of electrostatic charges, air buoyancy correction), recognition of "stability"*	PTB		

Inorganic Core Capabilities

Summary Table

CCQM Study : CCQM-K139 Elements in Human Serum

Institute(s) : NIM (Cl), PTB (Na)

Method : Ion chromatography (IC)

Analyte(s) : Na, Cl

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Contamination control and correction *All techniques and procedures employed to reduce potential contamination of samples as well as blank correction procedures. The level of difficulty is greatest for analytes that are environmentally ubiquitous and also present at very low concentrations in the sample.*		NIM, PTB	PTB: Sodium is present in all container materials and chemicals used. Cleaning and blank correction is very important.
Digestion/dissolution of organic matrices *All techniques and procedures used to bring a sample that is primarily organic in nature into solution suitable for liquid sample introduction to the ion chromatography system.*		NIM, PTB	PTB: Protein fragments from the serum proteins can cause severe interferences and elevated baselines. NIM: 0.2 g serum sample was added to ceramic vessel and heated at 500℃ for 5 hrs. After cooling to room temperature, 1 mL 5% HNO_3 was added to dissolve the residues, and diluted to 50 g for IC determination.
Calibration of analyte concentration *The preparation of calibration standards and the strategy for instrument calibration. Includes external calibration and standard addition procedures as well as the use of an internal standard.*		NIM, PTB	

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Signal detection *The detection and recording of the analyte signals. The degree of difficulty increases for analytes present at low concentrations.*	PTB		
Peak integration *Procedures used to determine peak areas. (e.g., high difficulty for small peak areas on complex or elevated baselines, especially in case of incomplete peak separation.)*		PTB	
Ion chromatographic separation *All efforts made to separate the analyte peak from other peaks. E.g. choice of eluent(s), isocratic/gradient elution, design of gradient, separation column parameters, type of stationary phase, temperature, flow, …*		PTB	
Dry mass correction *Choice and preparation/preconditioning of desiccant (drying agent), mass determination (control of electrostatic charges, air buoyancy correction), recognition of "stability"*	PTB		

Inorganic Core Capabilities

Summary Table

CCQM Study : CCQM-K139 Elements in Human Serum

Institute(s) : NIST (Cl)

Method : Micro-coulometry

Analyte(s) : Cl

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Contamination control and correction *All techniques and procedures employed to reduce potential contamination of samples as well as blank correction procedures. The level of difficulty is greatest for analytes that are environmentally ubiquitous and also present at very low concentrations in the sample.*		NIST	NIST: Chloride blanks were performed in acid solution prior to addition of serum sample. No carryover observed for repeat measures using blanks interspersed with serum SRM controls (909c and 956d).
Digestion/dissolution of organic matrices *All techniques and procedures used to bring a sample that is primarily organic in nature into solution suitable for liquid sample introduction to the ICP.*	NIST		
Digestion/dissolution of inorganic matrices *All techniques and procedures used to bring a sample that is primarily inorganic in nature into solution suitable for liquid sample introduction to the ICP.*	NIST		
Volatile element containment *All techniques and procedures used to prevent the loss of potentially volatile analyte elements during sample treatment and storage.*	NIST		

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Pre-concentration *Techniques and procedures used to increase the concentration of the analyte introduced to the ICP. Includes evaporation, ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*	NIST		
Vapor generation *Techniques such as hydride generation and cold vapor generation used to remove the analyte from the sample as a gas for introduction into the ICP.*	NIST		
Matrix separation *Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction, precipitation procedures, but not vapor generation procedures. Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*	NIST		
Calibration of analyte concentration *The preparation of calibration standards and the strategy for instrument calibration. Includes external calibration and standard additions procedures.*		NIST	NIST: Instrument response was calibrated for the amount of current delivered by the chloridometer against the high-precision coulometry system. A high-precision 100 Ω standard resistor connected to a high-impedance voltmeter (electrometer) was calibrated as a pair using the known current from the

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
			NIST coulometry system. Current readings were obtained to determine the average amount of current delivered per second and the rate of counts dr/dt (counts s^{-1}) was calibrated against a timer by initiating extended (>30 min) "dummy" titrations (without solution).
Signal detection *The detection and recording of the analyte isotope signals. The degree of difficulty increases for analytes present at low concentrations, of low isotopic abundance, or that are poorly ionized.*	NIST		
Memory effect *Any techniques used to avoid, remove or reduce the carry-over of analyte between consecutively measured standards and/or samples.*		NIST	NIST: Individual samples were analyzed in independent sample vials. Process blanks were performed at the start of each series of chloride titrations. Control samples (SRM 909c and 956d) performed on each day of analysis indicated no cross contamination occurred.
Correction or removal of isobaric/polyatomic interferences *Any techniques used to remove, reduce, or mathematically correct for interferences caused by mass overlap of analyte isotopes with isobaric or polyatomic species. Includes collision cell techniques, high resolution mass spectrometry, or chemical separations. The relative concentrations and sensitivities of the analyte isotopes and the*	NIST		

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
interfering species will affect the degree of difficulty.			
Correction or removal of matrix-induced signal suppression or enhancement *Chemical or instrumental procedures used to avoid or correct for matrix-induced signal suppression or enhancement.*		NIST	NIST: For each chloride value determined, a series of 7–9 serial chloride titrations were performed in the same sample vessel. A slight upward signal drift with sample addition was corrected by plotting sample addition (run order) as a function of Cl^- mass fraction. A linear drift correction was performed whereby the reported Cl^- mass fraction was the chloride mass fraction extrapolated back to zero sample.
Detector deadtime correction *Measurement of, and correction for, ion detector deadtime. Importance increases in situations where high ion count rates are encountered.*		NIST	NIST: To account for instrument response to chloride, current readings were calibrated at (5, 30, 60, 90, 120, and 180 s) following the initiation of current flow, to parallel the approximate period of time corresponding to the serum titrations. The mean of each set of six readings was taken as a single calibration.
Mass bias/fractionation control and correction *Techniques used to determine, monitor, and correct for mass bias/fractionation.*	NIST		

Inorganic Core Capabilities

Summary Table

CCQM Study : CCQM-K139 Elements in Human Serum

Institute(s) : NIM (Na)

Method : ETA-AAS (or GF-AAS)

Analyte(s) : Na

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
Contamination control and correction *All techniques and procedures employed to reduce potential contamination of samples as well as blank correction procedures. The level of difficulty is greatest for analytes that are environmentally ubiquitous and also present at very low concentrations in the sample.*		NIM	
Digestion/dissolution of organic matrices *All techniques and procedures used to bring a sample that is primarily organic in nature into solution suitable for liquid sample introduction to the ETA-AAS.*		NIM	NIM: 0.2 g human serum and 0.5 mL HCl were weighed and diluted to 50 g with deionized water. Then 2.0 g prepared solution was weighed with 0.6 mL HCl and diluted to approximate 60 g for Na determination with external calibration approach.
Digestion/dissolution of inorganic matrices *All techniques and procedures used to bring a sample that is primarily inorganic in nature into solution suitable for liquid sample introduction to the ETA-AAS.*			
Volatile element containment *All techniques and procedures used to prevent the loss of potentially*			

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
volatile analyte elements during sample treatment and storage.			
Pre-concentration *Techniques and procedures used to increase the concentration of the analyte introduced to the ETA-AAS. Includes evaporation, ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*			
Matrix separation *Techniques and procedures used to isolate the analyte(s) from the sample matrix to avoid or reduce interferences caused by the matrix. Includes ion-exchange, extraction, precipitation procedures, but not vapor generation procedures.*			
Hydride preconcentration/matrix separation of volatile species. *Coupling of a hydride system to the ETA-AAS and optimization of conditions.*			
Calibration of analyte concentration *The preparation of calibration standards and the strategy for instrument calibration. Includes external calibration and standard additions procedures. Also use of matrix-matched standards to minimize effect of interferences.*		NIM	
Signal detection *The detection and recording of the absorption signals of analytes. The degree of difficulty increases for analytes present at low concentrations, of low atomic absorption coefficient. Requires selection of operating conditions such*			

Capabilities/Challenges	Not tested	Tested	Specific challenges encountered
as light source, absorption line, Zeeman background correction conditions. Includes selection of signal processing conditions (peak area or height).			
Memory effect *Any techniques used to avoid, remove or reduce the carry-over of analyte between consecutively measured standards and/or samples.*			
Optimization of the furnace temperature program *Optimization of temperature and duration of steps for sample drying, pyrolysis to remove (residual) organics, and atomization. Furnace temperature program to minimize analyte loss in the drying/pyrolysis steps, while maximizing analyte vaporization in the atomization step.*		NIM	
Correction or removal of matrix effects or interferences *Chemical or instrumental procedures used to avoid or correct for spectral and non-spectral interferences. Includes effects of differences in viscosity and chemical equilibrium states of analyte between the standard and sample. Selection of matrix modifier to adjust volatility of analyte and/or matrix to eliminate these effects is also included. Addition of reactive gases (eg oxygen) to the carrier gas to improve matrix separation. Also included is Zeeman or other background correction techniques to remove interference due to absorption and scattering from coexisting molecules/atoms in the sample.*			