EURAMET Project 1165

Ion activity measurement of Na^+, K^+, Ca^{2+}, Mg^{2+} and Cl^- in water based mixed electrolyte samples

report of results

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1. Objective

The objective of this intercomparison is to demonstrate that SI-traceable chemical activities of the most relevant ions in physiological samples (namely those of sodium, potassium, calcium, magnesium and chloride) can be measured in a reliable way. The results gathered from the participating national metrology institutes, designated institutes and expert field laboratories provide a valuable contribution to the traceability of chemical activity measurement results in mixed electrolytes. Furthermore it helps to establish higher order reference standards and procedures for ion activity determination to be possibly used in the medical diagnostic area of the future (cf. IVDD 98/79/EG).
The interlaboratory comparison is organised in order to compare the measurement values and their assigned combined measurement uncertainties (the results), for the evaluation of the metrological performance of the developed measurement systems and procedures and finally helps for the mutual recognition of calibration and measurement data.

2. Scope

There is nowadays a growing awareness about the chemical form in which an element is present in biological systems. Qualitative and quantitative information on the element species and their interactions in biological systems is critical to understand their relevance to metabolic efficiency and impact on health. In clinical analysis, false positive or false negative results for the blood ion status of a patient can have dramatic consequences, especially in critical cases such as cancer, trauma or renal failure. The In-Vitro Diagnostic Directive (IVDD) 98/79/EC addresses the essential requirements that an in-vitro diagnostic device in the medical field must meet before being allowed to be marketed within the European Union. At present, the calibration methods that are implemented in medical diagnostics [2] do not make use of traceable ion activities – except the measurement of the pH value, as they consider the total concentration of each ion species, leading to considerable differences in abnormal conditions. The determination of ion activities and their related uncertainties is a prerequisite for the development of a valid traceable calibration method. Potentiometry using ion-selective electrodes (ISE) is the most frequent method for a direct measurement of the activity of ions. Unfortunately suitable, mixed standards with known traceability have been missing up to now for the calibration of the measurement equipment.
The intercomparison is a planned task in the EURAMET joint research project T2J10 *Tracebioactivity* (Grant Agreement No. 217257) [1]. The aims of the project are to:

- Build up a scale for chemical activity of clinical relevant ions which is consistent with the already existing and accepted activity scale for pH
- Establish systems for the measurement and calibration of chemical activity of ionic species in physiological matrices whose values are SI-traceable
- Provide a valuable contribution to the traceability of chemical activity measurements in mixed electrolytes by ISE.
- Establish higher order reference standards and procedures for ion activity as new diagnostic tools to support the IVD directive.

The interlaboratory comparison between the national metrology laboratories SMU, PTB and METAS and possibly other NMIs as well as selected expert laboratories is organised in order to compare the results and assess the quality of ion activity measurements in solutions that have a near physiological ion composition.

3. Test samples and standards

Two unknown synthetic, water based sample solutions will be provided by SMU. The solutions will be prepared from four chloride salts of known and sufficiently well characterised materials of sodium, potassium.. Assayed solutions will be used for magnesium and calcium as the direct preparation of the sample mixture starting from the alkaline earth salts is a delicate matter. The reference values of the purity and content of the four chloride salts are provided from SMU, based on coulometric chloride measurements:
NaCl: 99.71(14) %, KCl: 99.65(14) %, $MgCl_2 \bullet xH_2O$: 99.30(12) %, $CaCl_2 \bullet xH_2O$: 103.30(12) % (*k*=2).
Each sample solution will contain the five target ions Na^+, K^+, Ca^{2+}, Mg^{2+} and Cl^- approximately in the normal physiological range of amount of content (see table below), that will be analysed by each participant.
The ISE calibration standards containing the five ions will be prepared by each participant. The number of solutions is left open. A minimum of three solutions is recommended. The amount of content of each ion species in the standards should include the highest and lowest molality shown in the table below, as well as a level in between the boundary values.
Table: Molalities in the physiological range proposed for each ion species

Ion species	**Molality** ($mmol \cdot kg^{-1}_{water}$)
Sodium (Na^+)	130 - 150
Potassium (K^+)	3.0 - 5.0
Calcium (Ca^{2+})	0.7 – 1.75
Magnesium (Mg^{2+})	0.5- 1.2
Chloride (Cl^-)*	138 - 158

* note: the values for chloride are not in the physiological range

4. Ion-selective electrodes (ISE) measurement methods

The calculation of the reference values for molality will be performed by SMU, based on the gravimetric values of the preparation of standards. The ion activities are then determined based on the Pitzer model by convention and with an estimated uncertainty of 0.5 %.

Direct measurement of the ion activity:
As for pH, the ion activity measurement of other ions is and remains a method based on a convention.
The ion activity measurement results are to be referenced to a temperature of 20°C. Pitzer's approach is used to evaluate the ion activities for the standards. This semi-empirical approach is well accepted and tested and is in agreement with the accepted pH scale. The freeware program PHREEQC (from the USGS: http://wwwbrr.cr.usgs.gov/projects/GWC_coupled/phreeqc/) allows to calculate the activity of the standards. The uncertainties are evaluated separately using the ISO-GUM approach.

5. Reporting

All results for the activity of the five ions should be reported in $mmol \cdot kg^{-1}$ (active molality) together with a complete uncertainty statement according to the guide to the expression of the uncertainty in measurement (*GUM*, [5] This document is freely accessible now, cf.

below). Each laboratory result per sample and ion type x_i, is given as a mean value, however, with different standard deviation and a corresponding uncertainty $u(x_i)$. All results are considered independent random variables.

For each target ion measured, the membrane recipe with the ionophore (or ion exchanger) chosen should be specified, as well as the internal electrolyte concentration of the ISE and the external reference electrode. The relevant main performance characteristics or the type of potentiometer have to be reported. Additionally, the calibration slope is given in mV·decade^{-1} ($\left| \Delta\left[\log\left\{ \frac{a}{1\,\mathrm{mol}\cdot\mathrm{kg}^{-1}} \right\} \right] \right| = 1$) with the corresponding uncertainty as well as the ionic content for the 5 ions in the calibration standards (activity in mmol·kg^{-1}) with uncertainties. Standards have to be chosen and prepared so as to minimise the diffusion potential as well as their good match with the physiological ion composition. All the data for the standards including the detailed composition and source of the materials as well as the evaluated uncertainties are to be transmitted with the report.

The results of the comparison will be agreed on and only published on unanimous acceptance. The results of field and expert laboratories will be anonymised or not depending on the declaration of the participant. Confidentiality is assured and data will not be distributed without consent.

6. Participants

Participation in this comparison was open to metrology institutes and expert laboratories in this field.

EURAMET members:

CMI (CZ), METAS (CH), PTB (GE), SMU (SK)

Institutes not beeing EURAMET members:

- INMETRO,
Instituto Nacional de Metrologia, Normalizacão e Qualidade Industrial,
Labóratorio de Eletroquímica (DIMCI/DQUIM), [Brasil]

- NIMT,
National Institute of Metrology Thailand,
Environmental Research and Training Center (ERTC), [Thailand]

- ZHAW,
Zürcher Hochschule für Angewandte Wissenschaften,
Center for Chemical Sensors (CCS), [Switzerland]

- Industrial expert laboratory

(not disclosed), []

Table 1 Participating institutes and expert laboratories

Institute	Responsible Person	Ions measured	Remarks
CMI (Czech Republic)	Alena Vospělová Martina Vičarová	Na^+, K^+, Ca^{2+}, Cl^-	IC used
METAS (Switzerland)	Daniel Berdat Samuel Wunderli	Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-	organiser
PTB (Germany)	Frank Bastkowski Beatrice Adel Petra Spitzer	Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-	
SMU (Slovakia)	Michal Máriássy		prepared and distributed samples
NIMT (Thailand) Environmental Research and Training Center, ERTC	Sirinapha Srithongtim	Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-	IC used
INMETRO (Brasil) Electrochemistry Laboratory	Fabiano Barbieri Gonzaga	Na^+, K^+, Cl^-	
ZHAW (Switzerland) Zurich University of Applied Sciences, Wädenswil	Caspar Demuth	Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-	
Industrial expert laboratory	undisclosed	K^+, Ca^{2+}, Mg^{2+}	

Institutions and expert laboratories addresses

Sample preparation and calculation of reference values:

SMU, Slovakia
Slovak Institute Of Metrology
Contact person: **Michal Máriássy**
Address: Karloveska 63, SK-84255 Bratislava, Slovakia
Tel: +420 2 60 29 45 22
Fax: +420 2 60 29 45 61
e-Mail: mariassy@smu.gov.sk

Activity measurement

A. **METAS, Switzerland**

Swiss Federal Office Of Metrology
Contact person: **Samuel Wunderli**
Involved participants: **Hanspeter Andres; Daniel Berdat**
Address: Lindenweg 50, CH-3003 Bern-Wabern, Switzerland
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B. **PTB, Germany**

Physikalisch-Technische Bundesanstalt
Contact person: **Petra Spitzer**
Involved participants: **Beatrice Adel; Frank Bastkowski**
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Tel: +49 531 592 3130
Fax: +49 531 592 3015
e-Mail: petra.spitzer@ptb.de

C. **ZHAW, Switzerland**

Zürcher Hochschule für Angewandte Wissenschaften
Contact person: **Caspar Demuth**
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D. **CMI, Czech Republic**

Czech Metrology Institute, Regional inspectorate Brno
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Involved participant: Martina Vicarova
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Fax: +420 545 555 183
e-Mail: avospelova@cmi.cz

E. **NIMT (Thailand)**
Environmental Research and Training Center, ERTC
Contact person: **Sirinapha Srithongtim**
Address: Technopolis, Tambol Klong 5,
Amphoe Klong Luang,
Pathumthani 12120, Thailand
Tel: **+**66025774197
Fax: **+**66025774197
e-Mail: sirina.sri@gmail.com

F. **INMETRO, Instituto Nacional de Metrologia, Normalização e Qualidade Industrial, (Brasil)**
Labóratorio de Eletroquímica
Contact person: Fabiano Barbieri Gonzaga
Address: Av. Nossa Senhora das Graças 50 – Xerém, 25250-020 Duque de Caxias, RJ, Brasil
Tel: (21) 2679 9134
Fax: (21) 2679 9069
e-Mail: fbgonzaga@inmetro.gov.br

G. **Industrial laboratory**
undisclosed participant

Proposed program schedule

Deadline for registration:	September 17 2010
Shipment of samples:	October 22 2010
Deadline for reporting of results:	December 10 2010
Final report:	January 31 2011

Registration

To participate in this intercomparison exercise, the interested laboratories were asked to please contact the coordinating institute (METAS) for subscription by **September 17th 2010**.

7. Measurement procedure and equipment

Each participant used its own equipment and as well as its own calibration standards.

The expert at NIMT/ERTC used ion chromatography that is why METAS decided later on to perform an analysis of this type as well.

8. Reference values

The gravimetric values for ion molalities were evaluated by Michal Máriássy at SMU and were only supplied to the organiser after all the results were transmitted to him. From the ion molalities the reference values for the Pitzer ion activity were calculated using the USGS-program PHREEQC. The salts and solutions used to prepare the solutions had known, measured values for the puritities.

Solution1

(mmol.kg^{-1})	Na+	*U*(Na+)	K+	*U*(K+)	
Reference	**134.8**	0.01	**4.3956**	0.0001	molality
Reference	**103.3**	0.5	**3.296**	0.0015	activity

(mmol.kg^{-1})	Mg2+	*U*(Mg2+)	Ca2+	*U*(Ca2+)	
Reference	**1.0939**	0.0002	**0.9273**	0.0002	molality
Reference	**0.383**	0.002	**0.318**	0.002	activity

(mmol.kg^{-1})	Cl-	*U*(Cl-)	
Reference	**143.2**	0.03	molality
Reference	**106.2**	0.5	activity

Solution2

(mmol.kg^{-1})	Na+	*U*(Na+)	K+	*U*(K+)	
Reference	**140.2**	0.01	**3.660**	0	molality
Reference	**107.2**	0.5	**2.735**	0	activity

(mmol.kg^{-1})	Mg2+	*U*(Mg2+)	Ca2+	*U*(Ca2+)	
Reference	**0.869**	0.0002	**1.602**	0	molality
Reference	**0.301**	0.002	**0.543**	0	activity

(mmol.kg^{-1})	Cl-	*U*(Cl-)	
Reference	**148.8**	0.03	molality
Reference	**109.9**	0.5	activity

9. Results

molalities, not activities other values are activities

Solution1

(mmol.kg^{-1})	Na+	U(Na+)	Δref	Δ%	K+	U(K+)	Δref	Δ%	
Reference	**134.8**	0.01	0	0	**4.3956**	0.0001	0	0	molality
Reference	**103.3**	0.5	0	0	**3.296**	0.0015	0	0	activity
METAS	103.7	1.92	0.4	0.39	3.28	0.088	-0.016	-0.5	activity
PTB	103.1	2.64	-0.	-0.19	3.29	0.088	-0.006	-0.2	activity
INMETR	104.3	0.58	1.0	0.97	3.21	0.067	-0.086	-2.6	activity
ZHAW/CCS	106.9	2.6	3.6	3.48	3.14	0.09	-0.156	-4.7	activity
UDP	n.a.	.	.	.	3.01	0.04	-0.286	-8.7	activity
CMI	144.7	5.0	41.4	40	3.19	0.16	-0.106	-3.2	activity
METAS	134.5	0.8	-0.30	-0.22	4.38	0.04	-0.016	-0.35	**IC, molality**
NIMT/ERTC	132.5	6.6	-2.3	-1.7	4.32	0.079	-0.076	-1.7	**IC, molality**

Solution1

(mmol.kg^{-1})	Mg2+	U(Mg2+)	Δref	Δ%	Ca2+	U(Ca2+)	Δref	Δ%	
Reference	**1.0939**	0.0002	0	0	**0.9273**	0.0002	0	0	molality
Reference	**0.383**	0.002	0	0	**0.318**	0.002	0	0	activity
METAS	0.348	0.0083	-0.035	-9.1	0.313	0.0066	-0.005	-1.6	activity
PTB	0.382	0.018	-0.001	-0.26	0.298	0.018	-0.02	-6.	activity
INMETRO	n.a.	.	.	.	n.a.	.	.	.	activity
ZHAW/CCS	0.370	0.014	-0.013	-3.4	0.316	0.012	-0.002	-0.6	activity
UDP	0.291	0.027	-0.092	-24	0.275	0.001	-0.043	-14	activity
CMI	n.a.	.	.	.	0.436	0.023	0.118	37	activity
METAS	1.08	0.03	-0.014	-1.3	0.95	0.02	0.02	2.4	**IC, molality**
NIMT/ERTC	0.93	0.024	-0.164	-15	0.81	0.035	-0.12	-13	**IC, molality**

Solution1

(mmol.kg^{-1})	Cl-	U(Cl-)	Δref	Δ%	
Reference	**143.2**	0.03	0	0	molality
Reference	**106.2**	0.5	0	0	activity
METAS	106.6	2.22	0.4	0.38	activity
PTB	105.8	2.86	-0.4	-0.38	activity
INMETRO	105.9	0.69	-0.3	-0.28	activity
ZHAW/CCS	105.1	3.6	-1.1	-1.0	activity
UDP	n.a.	.	.	.	activity
CMI	127.61	0.21	21	20	activity
METAS	141	5	-2.2	-1.5	**IC, molality**
NIMT/ERTC	138.8	8.1	-4.4	-3.1	**IC, molality**

Solution2

(mmol.kg^{-1})	Na+	U(Na+)	Δref	Δ%	K+	U(K+)	Δref	Δ%	
Reference	**140.2**	0.01	0	0	**3.660**	0.0001	0	0	molality
Reference	**107.2**	0.5	0	0	**2.735**	0.0015	0	0	activity
METAS	108.6	2.0	1.4	1.3	2.73	0.063	-0.005	-0.18	activity
PTB	107.1	2.86	-0.1	-0.09	2.74	0.07	0.005	0.18	activity
INMETRO	107.4	0.6	0.2	0.19	2.65	0.064	-0.085	-3.1	activity
ZHAW/CCS	109.0	2.7	1.8	1.7	2.89	0.09	0.155	5.7	activity
UDP	n.a.	.	.	.	2.44	0.023	-0.30	-11	activity
CMI	135.1	6.3	27.9	26	4.94	0.23	2.21	81	activity
METAS	139.8	0.8	-0.40	-0.29	3.64	0.04	0	-0.55	**IC, molality**
NIMT/ERTC	134.7	6.7	-5.5	-3.9	3.61	0.054	0	-1.4	**IC, molality**

Solution2

(mmol.kg^{-1})	Mg2+	U(Mg2+)	Δref	Δ%	Ca2+	U(Ca2+)	Δref	Δ%	
Reference	**0.869**	0.0002	0	0	**1.602**	0.0002	0	0	molality
Reference	**0.301**	0.002	0	0	**0.543**	0.002	0	0	activity
METAS	0.339	0.0077	0.038	13	0.527	0.012	-0.016	- .0	ctivity
PTB	0.293	0.013	-0.008	-2.7	0.553	0.036	0.01	1.8	activity
INMETRO	n.a.	.	.	.	n.a.	.	.	.	activity
ZHAW/CCS	0.309	0.013	0.008	2.7	0.522	0.021	-0.021	-4.0	activity
UDP	0.246	0.022	-0.055	-18	0.422	0.015	-0.121	-29	activity
CMI	.	.	.	.	0.628	0.037	0.085	14	activity
METAS	0.86	0.03	-0.009	-1.0	1.65	0.02	0.048	3.0	**IC, molality**
NIMT/ERTC	0.75	0.024	-0.12	-14	1.53	0.056	-0.072	-4.5	**IC, molality**

Solution2

(mmol.kg^{-1})	Cl-	U(Cl-)	Δref	Δ%	
Reference	**148.8**	0.03	0	0	molality
Reference	**109.9**	0.5	0	0	activity
METAS	109.7	2.24	-0.2	-0.18	activity
PTB	109.5	3.16	-0.4	-0.37	activity
INMETRO	109.4	0.63	-0.5	-0.46	activity
ZHAW/CCS	109.0	3.7	-0.9	-0.83	activity
UDP	n.a.	.	.	.	activity
CMI	130.63	0.32	20.73	16	activity
METAS	149	5	0.2	0.13	**IC, molality**
NIMT/ERTC	144.0	7.8	-4.8	-3.2	**IC, molality**

10. References

[1] EURAMET Joint Research Project T2J10 Tracebioactivity, i-MERA-Plus Grant Agreement No. 217257. http://www.euramet.org/index.php?id=jrps

[2] Directive 98/79/EC of the European Parliament and the council on in vitro diagnostic medical devices, Official Journal of the European Communities, L331, 1-37, (1998).

[3] Samuel Wunderli, Hanspeter Andres: Metrological Aspects of Activity Measurements in Mixed Electrolytes by Ion-Selective Electrodes, Electroanalysis, 20, (3), pp. 234-330, (2008).

[4] Daniel Berdat, Hanspeter Andres, Samuel Wunderli: Development of Suitable ISE Measurement Procedures for SI-Traceable Chemical Activity Determination, Chimia, 63, (10), 670-677, (2009).

[5] *Guide to the Expression of Uncertainty in Measurement* **1995**, 1, International Organization for Standardization http://www.bipm.org/utils/common/documents/jcgm/JCGM_100_2008_E.pdf.