Director’s Report on the Activity and Management of the International Bureau of Weights and Measures

Supplement: Chemistry Department

(1 January 2015 – 31 December 2015)
BIPM Chemistry Department
Director: R.I. Wielgosz
(1 January 2015 to 31 December 2015)

1. **Gas metrology programme** (J. Viallon, E. Flores, P. Moussay, F. Idrees, T. Choteau and R.I. Wielgosz)

1.1 Greenhouse gases standards

1.1.1 *Key comparison on methane standards (CCQM-K82)*

A paper demonstrating equivalence between standards made in whole and synthetic air and measured by cavity ring-down spectroscopy (CRDS) and gas chromatography – flame ionization detection (GC-FID) for atmospheric monitoring applications was published in *Analytical Chemistry* in February 2015, completing activities related to CCQM-K82.

1.1.2 *Preparation for the key comparison on carbon dioxide (CCQM-K120)*

The BIPM developed innovative software to control, perform spectral acquisition and on-line analysis using Fourier Transform Infrared Spectroscopy (FTIR) and the MALT programme, and purchased a CO$_2$ Isotope Ratio Infrared Spectroscopy (IRIS) system. Both FTIR and IRIS systems were validated successfully using a set of 23 standards produced by NIST, NPL, and NOAA (the WMO-GAW Central Calibration Laboratory, CCL, for CO$_2$). The standards were produced using five different sources of CO$_2$ resulting in a rich diversity of δ$^{13}$C and δ$^{18}$O values which were useful for verifying both techniques under conditions that could be expected during an international comparison. The isotopic composition in at least one standard per CO$_2$ source was value assigned on the VPDB/J-RAS06 scale by the Max Planck Institute for Biogeochemistry (MPI-BGC) in Jena, Germany, being the WMO-GAW CCL for stable isotopes in CO$_2$, and/or the Institute of Arctic and Alpine Research - Geography University of Colorado Boulder (INSTAAR). A new paper describing this work entitled “FTIR and IRIS calibration strategies for accurate CO$_2$ in air mole fraction, δ$^{13}$C and δ$^{18}$O measurements” is being drafted and will be submitted to *Analytical Chemistry* in 2016.

In parallel, the assembly of the new manometric system for carbon dioxide measurements continued with the all-glass ensemble which was installed inside an oven maintained at 40°C and connected to a glass trap immersed inside a temperature controlled cryostat. Series of tests were performed, starting with leak detection and sealing, improvement of the carbon dioxide cryogenic trapping using the Residual Gas Analyser to monitor efficiency, and first measurements of the carbon dioxide amount separated from a known mixture in air. This work was supported by the secondment of Dr Steven Maxwell to the BIPM from the NIST, USA.

1.2 Air quality gas standards

1.2.1 *Ongoing ozone photometer comparison and calibration programme (BIPM.QM-K1)*

In 2015, three laboratories brought or sent their ozone national standards to the BIPM for comparison with the BIPM-SRP27 reference standard as part of the key comparison BIPM.QM-K1; the NIST in July, and the VSL, the Netherlands, in November. An additional comparison was performed with the Office of Environment and Heritage NSW, Australia, and published as a BIPM report. All reports of comparisons performed in 2014 have been published.
1.2.2  

**Ozone absorption cross-section value**

The new value of the ozone absorption cross-section measured by spectroscopy on pure ozone samples at the BIPM in 2014 was published in early 2015 in *Atmospheric Measurement Techniques*. Results were presented to the CCQM Working Group on Gas Analysis (GAWG), together with a proposal to create a task group to review all published values of ozone absorption cross sections at 254 nm, and provide a recommendation on the best value and uncertainty to be used, as a first step in the process of implementing a new cross section value globally. Dr Joseph Hodges (NIST) has accepted the role of chairing the group, with an expected starting date of early 2016.

Meanwhile a paper giving details of the results obtained in 2015 with the gas phase titration (GPT) system is in preparation. All tests and measurements have been completed using the new reaction chamber, including FTIR analysis of the standard mixtures of nitrogen monoxide (NO) and nitrogen dioxide (NO₂) purchased in 2014. The presence of nitric acid was observed in nitrogen dioxide mixtures, at mole fractions larger than certified. Taking this correction into account, the titration of ozone traceable to either NO or NO₂ gravimetric standards resulted in good agreement, whilst the disagreement with ozone measured by UV photometry was confirmed. Final results are being used to deduce a GPT-based value of the ozone cross-section, with an uncertainty comparable to measurements performed in 2014 on pure ozone samples.

1.2.3  

**Key comparison on formaldehyde standards (CCQM-K90)**

The comparison started in December 2014 with the measurement of the formaldehyde mole fraction in all 14 transfer standard cylinders against the BIPM dynamic generation system based on permeation of paraformaldehyde. After two series of measurements, two more were performed against the second system based on trioxane diffusion. In April 2015 a subset of eight cylinders were selected and sent to participants. Meanwhile the other six cylinders were regularly measured at an average frequency of one series of measurements per month in order to monitor their stability. Participants performed their own measurements between June and October. Cylinders are to be returned to the BIPM, where they will again be analysed together with the other six, against the two dynamic generation systems. The results will be presented to the GAWG in April 2016.

1.2.4  

**Preparation for a repeat key comparison on nitrogen dioxide (CCQM-K74.2018)**

Following on from the initial discussion on “Future comparisons and pilot studies for the GAWG - Core KC (NO) and spectroscopy PS”, in April 2015 at the BIPM, the GAWG decided that the pilot study on spectroscopy is to be moved to a comparison timetable to coincide with the NO₂ key comparison planned for 2017. The NO₂ key comparison is to have the number [CCQM-K74.2017](https://www.cccm.org/cccsm/cccqm). This comparison will be designed to evaluate the consistency of primary NO₂ gas standards from National Metrology Institutes at the µmol mol⁻¹ level.

1.2.5  

**Preparation for the key comparison on nitrogen monoxide (CCQM-K137)**

Planning for a key comparison on nitrogen monoxide (NO) at 30-70 µmol/mol in nitrogen, to commence in late 2016, was discussed in April 2015 within the GAWG. The comparison will be a repeat of the earlier CCQM-P73 pilot study that was coordinated by the BIPM. The facility developed for the pilot study has been re-validated in 2015 after the acquisition of new NO standards to underpin the GPT system. An agreement better than 0.05 µmol mol⁻¹ between a set of ten standards from two different NMIs prepared between 2009 and 2015 was demonstrated. Twenty laboratories have expressed an interest in participating in the future comparison.
1.2.6 Gas metrology programme quality system

A new procedure covering the comparison and calibration of nitrogen monoxide in nitrogen standards was added to the Quality System that underpins the Gas Metrology work programme. The system was reviewed during an internal audit undertaken in November 2015. No major non-conformities in the documentation and implementation were reported by the auditors. A series of actions to address minor non-conformities and observations raised in the audit report will be undertaken in 2016.


2.1 Purity methodology and small molecule purity analysis

The approach to the use of data from organic purity assignment comparisons coordinated by the BIPM described in a “White Paper” prepared by the BIPM was implemented in 2015 by the CCQM Working Group on Organic Analysis (OAWG) and the CCQM Working Group on Key Comparisons and CMC Quality (KCWG).

The BIPM has continued to coordinate an International Union of Pure and Applied Chemistry (IUPAC) working group, with members from 12 NMIs and two international organizations. Two further meetings were held in 2015 to draft technical guidelines on ‘Methods for the SI Value Assignment of the Purity of Organic Compounds for use as Primary Reference Materials and Calibrators’. The BIPM organized and hosted the third meeting of the working group in April 2015. The final Technical Report from this working group will be produced in 2016.

2.2 NMR work programme

Following the official opening of the BIPM qNMR facility in November 2014 and handover of the 400 MHz spectrometer by the manufacturer, qualification and acceptance testing of the spectrometer were successfully undertaken at the BIPM at the beginning of 2015. An extended visit to the BIPM by Dr Takeshi Saito, NMIJ, Japan, in February 2015 discussed the BIPM-NMIJ collaboration in this area and provided further training to BIPM staff.

Scientists from NIM, China, and UME, Turkey, have worked on secondment at the BIPM in 2015 to develop and validate methods for performing high accuracy qNMR measurements in various deuterated solvents. As a result of this ongoing programme the measurement equation for organic purity determinations by qNMR is being investigated and the major influence factors for qNMR analysis identified.

The qNMR facility was used internally for the first time to assign a purity value to the CCQM-K55.d comparison material, folic acid.

2.3 Organic programme quality system

The actions to address minor non-conformities and observations raised as a result of an External Audit in 2014 were implemented and finalized in 2015. The Quality System that underpins the Organic Work Programme was reviewed during an Internal Audit in December 2015. No non-conformities were identified as a result of this latest Audit.
2.4 Purity comparison CCQM-K55.d [Folic acid]

The characterization of the CCQM-K55.d candidate material (folic acid) was completed at the BIPM using both mass balance and qNMR methods. The comparison protocol and call for participation was circulated to the OAWG in July 2015. Seventeen NMIs and DIIs have registered to participate in CCQM-K55.d and an additional six participants, including three authorized guest laboratories, have registered for the CCQM-P117.d parallel pilot study. The comparison samples were distributed to participants in September 2015 and the submission of results is scheduled for January 2016.

2.5 Calibration solution comparison CCQM-K78 [Amino acids in aqueous solution]

Validation studies for methods for the assignment of the mass fraction content of amino acids in solution using LC-UV, LC-CAD, LC-MS/MS and IC were completed in 2015. These were required for the CCQM-K78 comparison that will be coordinated by the BIPM. The validation studies were successfully completed during a project undertaken at the BIPM in 2015 by a scientist on secondment from INMETRO, Brazil.

A candidate material consisting of a batch of 200 ampoules of a multi-component amino acid solution has been prepared and will be evaluated for suitability as the CCQM-K78 comparison material in 2016.

2.6 Organic large molecule purity – Angiotensin I, Insulin, Hepcidin, Oxytocin and Calcitonin model studies

The development and validation of a range of analytical methods for the purity determination of the intact decapptide angiotensin I (ANG I) and insulin (INS) was completed by the BIPM. The BIPM has successfully finalized the cross-validation of different approaches for the purity mass fraction value assignment for both model peptides ANG I, in collaboration with the NIST, and INS. The methods developed are to be used in the CCQM key comparison on peptide purity. One external publication describing the development and comparing mass spectrometric methods for the quantification of ANG I was published. External publications on the final results of both ANG I and INS are in preparation.

Ms P. Bros from the LNE joined the BIPM as visiting scientist, as part of her PhD study, to work on the method development for high resolution mass spectrometry coupled to liquid chromatography (LC-hrMS) for the purity determination of hepcidin, a key regulator of iron homeostasis and a promising clinical biomarker for brain iron deposition, which is implicated as a potential cause of Alzheimer’s disease.

In collaboration with the NIM, China, high-purity oxytocin and calcitonin, both synthetic therapeutic peptides, have been produced, and will be used to investigate their suitability to serve as future key comparison materials as potential model systems for small peptides with disulfide bonds.

2.7 Organic large molecule purity – Human C-peptide

The first CCQM key comparison on peptide purity (CCQM-K115/P55.2) coordinated by the BIPM in collaboration with the NIM, China, was launched. Dr M. Li from the NIM joined the BIPM as a visiting scientist to continue the work on method development and to study material characterization for the key comparison.

The assignment of the mass fraction content of high-purity C-peptide (hCP) has been accepted as the most appropriate choice for a first CCQM key comparison that will investigate competencies to perform peptide purity mass fraction assignment. hCP was chosen as a model system from which performance of other molecules can be inferred, whilst simultaneously focusing on a material directly relevant to existing CMC claims.
hCP is an important clinical and forensic analyte in its own right, for which accurate reference measurement systems are required. It is a chemically-synthesized linear peptide of known sequence, without cross-links, that contains 31 amino acids. It will directly support NMI services and certified reference materials (CRMs) which are currently provided by NMIs.

The impurity profile of the batch and the outcome of the homogeneity and stability studies have been found to be appropriate for the purposes of the comparison. The study samples were shipped to the participants and the key comparison and a parallel pilot study began in early December 2014.

The participants reported their assignments of the mass fraction content of the high-purity hCP prior to September 2015. Different methods were used by the participants. The PICAA analysis approach, requiring quantification of constituent amino acids following hydrolysis of the material and correction for amino acids originating from impurities, has been used by the majority of participants. Peptide related impurities have been determined mainly by LC-hrMS. The coordinating laboratories (BIPM and NIM) have used the mass balance approach employing a variety of analytical methods, such as LC-hrMS, GC-MS, KFT, TGA and IC. In addition, qNMR and CHN elemental analysis, both with correction for amino acids originating from impurities, have been used.

A first discussion of the results took place during the fall meeting of the new CCQM Working Group on Protein Analysis (PAWG) in October 2015.

3. **Activities related to the JCTLM** (S. Maniguet and R.I. Wielgosz)

Dr Wielgosz is the Executive Secretary of the Joint Committee for Traceability in Laboratory Medicine (JCTLM), the leader of its review team on Quality Systems and Implementation, and a member of the JCTLM Working Group for Education and Promotion on Traceability (WG-TEP). Dr Maniguet coordinates the development of the JCTLM Database, and is a member of the review team on Quality Systems and Implementation, and the Secretary of the JCTLM WG-TEP.

In February 2015, the WG1 Cycle 11 reference materials, and measurement methods, and WG2 Cycle 9 reference measurement laboratory services approved by the Executive Committee during its 13th Annual Meeting in December 2014 were published in the database.

As of December 2015 the JCTLM Database contained:

- 295 available certified reference materials that cover 11 categories of analytes. Of these reference materials, 33 are in List II, which includes reference materials that are value-assigned using internationally agreed protocols, and three are in List III, which covers reference materials with nominal properties;
- 176 reference measurement methods or procedures that represent about 80 different analytes in nine categories of analytes;
- 133 reference measurement services, delivered by fourteen reference laboratories and two NMIs in eight countries and which cover seven categories of analytes.

The WG1 Cycle 12 call for nominations of higher order reference materials and reference measurement methods or procedures, and the WG2 Cycle 10 call for nominations of reference measurement laboratory services were announced on the JCTLM website in February 2015, and email notifications were sent to about 400 potential contributors to the JCTLM. As of July 2015, 19 nominations for materials, six nominations for methods, and 27 nominations for services had been received and sent to the review teams for their evaluation.

The second issue of the JCTLM Database Newsletter was edited in collaboration with the ILAC Marketing Office, and distributed by email in March 2015 to the JCTLM contact list maintained at the BIPM. Future editions of the Newsletter will benefit from the contributions of the JCTLM TEP-WG.
A web-based form was made available on the database website from December 2014 to January 2015 to determine the profile of users of the database. A total of 85 responses were collected and evaluated, of these 34 % were from clinical laboratories, 20 % from IVD manufacturers, 20 % from Reference Laboratories, 8 % from NMIs/ DIs, 3 % from accreditation (regulatory) bodies, and the remainder from other organizations.

The database log-on analysis carried out over 2015 indicated that the number of visits to the website was 1400 on average per month.

The 14th and 15th meetings of the Executive Committee of the JCTLM were held at the BIPM on 25-26 June 2015, and on 3-4 December 2015, respectively. During its meeting in December, the Executive approved the revised text of the Declaration of Cooperation (DoC) between the BIPM, IFCC and ILAC, and its Appendices. The amendments made to the text followed the recommendation from the ad hoc Working Group on JCTLM Governance to open the Executive to more international organizations and bodies with a clear interest in promoting reliable, comparable and traceable measurements in clinical chemistry and laboratory medicine. It aims to create a new JCTLM Members Stakeholder category in addition to the National and Regional Members category, and to merge the WG1 (materials and methods) and WG2 (services) into a unique Database Working Group structured according to specific group of analytes.

The JCTLM Members’ and Stakeholders’ meeting held at the BIPM on 31 November and 1 December 2015 brought together 65 attendees from the In Vitro Diagnostic Industry, as well as from the clinical chemistry and laboratory medicine community. The meeting included five sessions: “Update on JCTLM activities”, “JCTLM Member activities”, “Developments in Traceability Requirements around the Globe”, “Identifying future priorities in Traceability in Laboratory Medicine”, and “New Challenges for Traceability in Laboratory Medicine”.

The inaugural meeting of the JCTLM Working Group for Education and Promotion on Traceability, and the annual meeting of the JCTLM Working Group 1 and 2 were held at the BIPM on 2 December 2015. The new structure of the database WG was trialled during the review process in 2015, and the vice-Chairs of the WG together with the leaders of the review teams reported directly during the meeting on their recommendations resulting from their technical assessment of the material, method, and service nominations. The next step will be to revise the procedure documents of the JCTLM Quality Manuals to describe the process.

ISO TC 212 WG2 is continuing the revision of two normative standards of particular importance to the JCTLM processes, notably ISO 17511 and ISO 15195. The BIPM participates actively as a liaison organization to ISO TC 212.

4. Publications


5. **Activities related to the work of Consultative Committees**

The CCQM held its 21st meeting on 20-21 April 2015 at the BIPM. It was preceded by meetings of the CCQM Working Groups.

R.I. Wielgosz is the Executive Secretary of the CCQM and a member of the CCQM Strategic Planning Working Group (SPWG).

J. Viallon is a member of the CCQM Working Group on Gas Analysis (GAWG).

E. Flores is a member of the CCQM Working Group on Gas Analysis (GAWG).

S. Westwood is a member of the CCQM Working Group on Organic Analysis (OAWG).

R. Josephs is a member of the CCQM Working Group on Protein Analysis (formerly part of the CCQM Working Group on Bioanalysis (BAWG)), the CCQM Working Group on Organic Analysis (OAWG) and the *ad hoc* Steering Group on Microbial Measurements (MBSG).

S. Maniguet is a member of the CCQM Working Group on Key Comparisons and CMC Quality (KCWG).

6. **Activities related to external organizations**

R.I. Wielgosz is a BIPM representative to the International Union of Pure and Applied Chemistry, Interdivisional Committee on Terminology, Nomenclature and Symbols (IUPAC ICTNS), ISO TC 212, Clinical laboratory testing and *in vitro* diagnostic test systems, Working Group 2 on Reference Systems, and ISO TC 146 on Air Quality, and is a member of the editorial board of Accreditation and Quality Assurance. He is a member of the World Meteorological Organization (WMO)-BIPM Joint Liaison Group.

J. Viallon is the BIPM representative at ISO TC 146/SC 3 on Air Quality – Ambient Atmospheres.
S. Westwood is the chair of the IUPAC Project 2013-025-2-500: Methods for the SI Value Assignment of Purity of Organic Compounds, the BIPM liaison to both the ISO/REMCO and the REMCO/CASCO Joint Working Group 43 and a member of the World Anti-Doping Agency (WADA) Laboratory Expert Group.

R. Josephs is the BIPM representative to the Inter-Agency Meeting and the Codex Committee on Methods of Analysis and Sampling (CCMAS) of the Codex Alimentarius Commission.

7. Travel in 2015

R.I. Wielgosz to:
- Malta, 5-6 February, to present on BIPM activities at the EURAMET METCHEM meeting.
- Münster (Germany), 23-25 February, to give an invited lecture on the JCTLM at the European Winter Conference on Plasma Spectrochemistry (EWCPS).
- NIM (China), 2-6 March 2015, invited visit to the NIM laboratories and for mutual presentations of activities in chemistry metrology.
- College of American Pathologists, Chicago (USA), 7-9 April, to participate in ISO TC 212 WG2 meetings.
- Paris (France), 24 June, to give JCTLM lecture at the Euromedlab conference.
- Rotterdam (the Netherlands), 10-12 June 2015, to Chair a session on Metrology and Standardization at the GAS2015 conference.
- Boston (USA), 19-20 August, to give presentations on CCQM activities and the redefinition of the mole at the ACS conference.
- Max-Planck-Institute for Biogeochemistry, Jena (Germany), 26-27 August, to visit the Institute and to give an invited lecture.
- NIST, Gaithersburg (USA), 19-20 October 2015, to contribute to the CCQM PAWG/OAWG meetings.
- IRMM, Geel (Belgium), 10-13 November, for ISO TC 212 Plenary and WG2 meetings.
- UNIDO, Vienna (Austria), 17 December, to give a presentation on the Mycotoxin Metrology CB&KT programme.

J. Viallon to:
- OECD, Paris (France), 4 February 2015, to attend the Meeting of the Working Party on Manufactured Materials (WPMN).
- Rotterdam (the Netherlands), 10-12 June 2015, to attend the GAS2015 conference.
- NIM (China), 2-6 March 2015, invited visit to the NIM laboratories and for mutual presentations of activities in chemistry metrology.
- SIO, La Jolla, (USA), 13-17 September 2015, to attend the 18th WMO/IAEA Meeting on Carbon Dioxide, Other Greenhouse Gases, and Related Measurement Techniques (GGMT-2015).

E. Flores to:
- Rotterdam (the Netherlands), 10-12 June, to attend GAS 2015 and to present the lecture: Use of FTIR for accurate comparisons of gas standards.
- Max-Planck-Institute for Biogeochemistry, Jena (Germany), 26-27 August, to visit the Institute.
- CENAM, Queretaro (Mexico), 23 September, to give the lecture: Use of FTIR for accurate comparisons of gas standards.
• CENAM, Queretaro (Mexico), 23-25 September, theoretical and practical training course on FTIR and MALT 5.

• Universidad Nacional Autónoma de México (UNAM), Mexico City (Mexico), 28 September, to present the lecture: “Comparaciones Internacionales de mezclas de gases primarios (CO₂, CH₄ y HCHO), realizadas con las técnicas FTIR, CRDS y GC-FID en el BIPM (Bureau International des Poids et Mesures)”.

S. Westwood to:

• Beijing (China), 2-6 March, for discussions on the BIPM and NIM metrology in chemistry programmes and potential future collaborations.

• Pretoria (South Africa), 14-17 June, for the 38th meeting of the ISO-REMCO.

• Geneva (Switzerland), 9-11 July, for the second meeting of the REMCO/CASCO Joint Working Group 43.

• National Harbour (USA), 11-15 October, to attend the 14th BERM Conference and give an oral presentation on the BIPM qNMR programme;

• Gaithersberg (USA), 16-20 October, for the meeting hosted at the NIST of the IUPAC Organic Purity Technical Report and CCQM Organic Analysis Working Groups.

• Montreal (Canada), December, for a meeting of the WADA Laboratory Expert Group.

N. Stoppacher to:

• Frankfurt (Germany), 7-9 April, for training on the theory and application of NMR.

R. Josephs to:

• IAM, Budapest (Hungary), 20 February, to represent the BIPM at the Inter-Agency Meeting of the Codex Alimentarius Commission.

• Foresight Centre, Liverpool (UK), 7-8 July, to participate in the Ionmobility-Mass Spectrometry meeting and workshop of British Mass Spectrometry Society (BMSS).

• BERM14, National Harbour (USA), 11-15 October, to give a presentation at the 14th Biological and Environmental Reference Materials conference.

• IUPAC, NIST, Gaithersburg (USA) 16 October, to contribute to the IUPAC purity meeting.

• NIST, Gaithersburg (USA), 19-20 October, to contribute to the CCQM PAWG/OAWG meetings.

• USP, Rockville (USA), 2-4 November, to attend the therapeutic peptide workshop and expert panel of the US Pharmacopeia.

8. Visitors in 2015

• T. Saito (NMIJ), 9-20 February 2015, for discussions on the BIPM-NMIJ qNMR project.

• K. Chiba (NMIJ), 12-13 February 2015.

• O. Rabin and V. Ivanova (WADA), 19 March 2015, for discussions on BIPM WADA collaborations.

• S. Assonov (IAEA), 15 April 2015.

• D. Griffiths (University of Wollongong), 20-21 April 2015.

• M. Ramonet, O. Laurent and L. Rivier (LSCE), 5 May 2015.

• J. Wheeler (NIBSC), 21 May 2015.

• J. Norris (NIST), 6-10 July 2015.
- V. Delatour and S. Vaslin-Reiman (LNE), 28 July and 21 September 2015, for discussions on the BIPM-LNE secondment.
- T. Suematsu (JEOL) and A. Mairu (WAKO), 25 September 2015, to discuss the BIPM-NMIJ qNMR project.
- O. Rabin and V. Ivanova (WADA), 28 October 2015, to discuss planning for the BIPM-WADA joint symposium on Anti-Doping Analysis in 2016.
- D. Heikens (VSL), 2-4 November 2015.

9. **Guest workers in 2015**

- M. Li, NIM (China), 1 January to 31 October.
- B. Garrido, INMETRO (Brazil), 2 February to 29 May.
- T. Huang, NIM (China), 9 March to 4 September.
- P. Bros, LNE (France), since 1 July.
- I. Un, UME (Turkey), 1 September to 27 November.
- S. Maxwell, NIST (USA), since 1 September.