Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM)

President: Dr W.E. May          Executive Secretary: Dr R.I. Wielgosz

1. Executive summary

The CCQM is responsible for metrology in chemistry and biology, and its activities between 2015 and 2018 are reported here. The Committee updated and published its strategy document in 2018, addressing the key challenges it faces in the broad and complex field in which it operates. With a portfolio of over 170 key comparisons and over 130 pilot studies to date, it manages these by operating through eleven Standing Working Groups and additional ad hoc groups being convened as needed. During this period, the Bioanalysis Working Group was subdivided into three working groups focused on protein, nucleic acid and cellular analysis, all of which have now implemented active comparison programmes. A working group on isotope ratios has been established in response to stakeholder needs, as well as a task group on method defined measurands, which has been asked to develop criteria for assessing which of the growing number of method defined measurands should be covered within the scope of activities of the CCQM.

During this reporting period, 48 CCQM Key comparisons were started as well as 11 stand-alone pilot studies, of which 9 key comparisons and 1 pilot study were being coordinated by the BIPM. These numbers compare well with the predicted 16 new comparisons which the CCQM foresees that it will start each year, and a reduction from the number predicted in our previous strategy document, attesting to the improvements in effectiveness from the adoption of a “core key comparison” model within CCQM which focuses more on interrogation of the skills and competencies maintained by NMI/DI’s to deliver services to their customers.

The CCQM has been active in consulting the global chemical community regarding the redefinition of the mole, and has worked with the International Union of Pure and Applied Chemistry (IUPAC) to develop wording regarding the new definition that is acceptable to both the metrology and practitioner communities.

The CCQM continues to provide a forum for exchange of information on technical activities. In the last five year period the CCQM WGs have organized sixteen workshops with the goal of exchanging information on research and development activities in chemical and biological measurement science. The CCQM 2017-2026 strategy document references twenty five publications in peer-reviewed journals that were stimulated or resulted from CCQM comparisons.

The broad range of activities covered by the CCQM is exemplified by the eleven impact case studies provided in our Strategy Document. The Studies describe the benefits and impact of internationally equivalent and traceable measurements in the healthcare, environmental monitoring, food safety, energy, and advanced manufacturing sectors.

2. Scope of the CC

The CCQM is responsible for developing, improving and documenting the equivalence of national standards (certified reference materials and reference methods) for chemical and biological measurements. It strives to progress the state of the art of chemical and biological measurement science and to work with global stakeholders to promote and increase the impact...
of metrology in chemistry and biology. It advises the CIPM on matters related to chemical and biological measurements including advice on the BIPM scientific programme activities.

The objectives of the CCQM are:

a. to progress the state of the art of chemical and biological measurement science (including contributing to the establishment of a globally recognized system of national measurement standards, methods and facilities for chemical and biological measurements; and acting as a forum for the exchange of information about the research and measurement service delivery programmes and other technical activities of the CC members and observers, thereby creating new opportunities for collaboration)

b. to reach out to new and established stakeholders (facilitating dialogues between the NMIs and global stakeholders in order to define new possibilities for metrology in chemistry and biology to deliver impact)

c. to demonstrate the global comparability of chemical and biological measurements (through promoting traceability to the SI, and where traceability to the SI is not yet feasible, to other internationally agreed references; contributing to the implementation and maintenance of the CIPM MRA with respect to chemical and biological measurements);

3. **Strategy**

The CCQM strategy document covering the period 2017 to 2026 was published on 17 January 2018. This follows on from a complete review and revision of the previous document covering the 2013-2023 period, the last version of which was published in July 2014. The detailed list of comparisons planned for the 2017 to 2026 period continues to be updated on a six monthly basis by the CCQM.

A major change to the document has been a restructuring to reflect the generic objectives for all Consultative Committees, notably: to progress the state of the art of measurement science; to reach out to new and established stakeholders; to demonstrate the global comparability of measurement standards.

The CCQM has continued to respond to three key challenges identified in the first strategy document, and thereby achieved the following:

1. in response to the requirement to maintain an efficient, effective and manageable programme of comparisons, it has continued to develop and implement the core capability approach to key comparisons, which has allowed the foreseen number of comparisons required annually to underpin NMI capabilities to be reduced to 16 from the 19 foreseen previously;

2. in response to the requirement deal with new, emerging and evolving fields, it has established active working groups with well-defined activities and comparisons for protein analysis, nucleic acid analysis and cellular analysis as well as establishing a new working group on isotope ratio measurements;

3. in response to the requirement to improve the efficiency of the CMC generation and review process, it has implemented the recommendations for the CIPM MRA review, including starting implementation of broad claim CMCs, and has seen the growth rate in the total number of CMCs related to chemical/biological measurements reduce.
The CCQM will continue to provide a forum for information exchange on leading edge measurement research activities. Mechanisms for achieving this include:

a) Technical presentations as part of the CCQM WG activities
b) Focused workshops on cutting edge measurement science research within the CCQM WGs
c) Sector specific workshops organized by the CCQM
d) Support of workshops with RMOs, NMIs and Stakeholders (e.g. Protein and Peptide Therapeutics and Diagnostics PPTD-2018, organized with BIPM, NIM and JCTLM)

The CCQM has a long history in the organization of workshops with stakeholder and sectorial groups in order to understand their requirement for accurate and traceable measurement results and guide the work of the CCQM working groups (including the fostering of new working groups as appropriate). In addition, several BIPM organized workshops have provide further contact with stakeholders important to CCQM, notably:

• BIPM Workshop on Global to Urban Scale Carbon Measurements, 30 June-1 July 2015;
• BIPM-NIM workshop on Protein and Peptide Therapeutics and Diagnostics, 1-3 June 2016 and 10-12 October 2018;
• BIPM-WADA Symposium on Standards and Metrology in support of Anti-Doping, 28-29 September 2016.

The CCQM will continue to work with international stakeholders with specialist workshops and when further collaboration is required, as well as invitations to participate in meetings of the CCQM WGs (e.g., IAEA, WMO, WHO/NIBSC, national and regional Pharmacopeias, such as USP and EDQM) or the CCQM (e.g., IUPAC, WMO, WADA, Codex Alimentarius, WHO, IFCC, ENFSI, ISO/REMCO, ILAC, VAMAS).

4. **Activities and achievements since the last meeting of the CGPM**

4.1. **Comparisons and CMCs**

The total number of NMIs/DIs providing Chemical and Biological CMCs is 61 (50 in 2012) from 48 different countries (39 in 2012). The total number of Chemical Biological CMCs in the BIPM KCDB is 6412 (October 2018) from 5718 in 2014. In the period 2015-2018, 48 CCQM Key comparisons were started as well as 11 stand-alone pilot studies, of which 9 key comparisons and 1 stand-alone pilot study are coordinated by the BIPM, to underpin these capabilities.

4.2. **Impact Studies and Stakeholder Engagement**

Eleven case studies have been reported in the CCQM 2017-2026 strategy document to highlight the impact of CCQM activities and their links to stakeholders. The benefits and impact of internationally equivalent measurement are described for examples in:

- Healthcare
- Environmental Monitoring
- Food Safety
- Energy
- Advanced Manufacturing
- Redefinition of the SI units
The comparisons led by the CCQM WGs have contributed to the following examples of achievements

- **Improved accuracy and quality assurance for Vitamin D measurements worldwide.** In CCQM-K132 metrology institutes demonstrated their capabilities for the measurement of vitamin D metabolites in two different serum pools. All participants demonstrated the capability of determining the main metabolite, 25(OH)D3, at levels ~25 ng/g with a CV of 3%. This comparison underpins critical programs covering the production of certified reference materials and the complementary provision of reference values for External Quality Assurance Schemes, for Vitamin D that has been described as the “Vitamin of the decade” with a growing list of adverse health outcomes linked to its deficiency. Vitamin D is being studied for its possible connections to conditions such as diabetes, hypertension, autoimmune diseases, bone disorders and some types of cancer. High levels of Vitamin D can also be toxic and lead to a range of symptoms with excess vitamin D reported to lead to damage to the kidneys. As a result, over the last decade there has been a world-wide increase in the level of vitamin D testing.

- **Support for standardization of diabetes diagnostics.** The CCQM-K115 key comparison allowed nine NMIs to compare their capabilities for value assigning C-peptide primary reference materials, a biomarker for natural insulin production. This has supported the development of a reference measurement system for C-peptide measurements, which will allow standardization of IVD measurements globally, and thereby providing improvements in diabetes diagnostics and management, a condition currently affecting over 450 million adults worldwide.

- **Supporting regulations for improvements in water quality.** Chemical pollution from pharmaceutical residues in water supplies poses a threat to the aquatic environment and human health, and this phenomenon has become one of the major emerging environmental issues in recent decades. CCQM-K126 addressed reference methods for the measurements of pharmaceuticals in surface water, focusing on carbamazepine, at levels relevant to regulatory limits. This provides accurate assessment methods for measuring hazardous substances in surface waters which have been highlighted as indispensable tools to safeguard the environment and the public health. With increasing water reuse and recycling the assessment of levels of compounds like pharmaceuticals in water will continue to be a high priority. Institutes that successfully demonstrated their capabilities in this comparison will have an international benchmark to underpin services they are able to offer across the broader classes of similar types of contaminants in water supplies.

- **Providing new standards to monitor greenhouse gas emissions and their sources.** The equivalence of the next generation of CO2 in air standards was addressed in the CCQM-K120.a and b comparisons, during which 46 standards were compared. The comparison supports the development of the next generation of greenhouse gas standards, which will be valued assigned for CO2 mole fraction and isotope ratio and matrix matched to atmospheric compositions, providing instrument manufacturers and atmospheric scientists with the standards required to monitor CO2 mole fractions and isotope ratios accurately in real time. The activities have improved the state of the art in measurement science, benchmarked comparability and supported NMIs in working towards addressing the needs of stakeholders, which will permit the identification of sources and
sinks of carbon at local, regional, and global scale, and contribute to the understanding of their relative impacts on atmospheric concentrations.

- **Food Safety**. CCQM coordinated a specific key comparison CCQM-K103 “Melamine in Milk Powder” to demonstrate the capability of NMIs/DIs to provide accurate measurements for traces of melamine in milk and milk powder. Melamine (1, 3, 5-triazine-2, 4, 6-triamine), with its high nitrogen content, has been unethically added to food products in order to increase their apparent protein content. The melamine incidents that occurred as a result of tainted pet food in the United States in 2007 and tainted milk powder in China in 2008 caused significant impact. After these crises, the analysis of melamine in food has become one of the important routine measurements for food testing laboratories. The key comparison assisted in ensuring the comparability of reference measurement procedures being used internationally to produce certified reference materials for food laboratories. In addition, several NMIs/DIs have been coordinating proficiency testing (PT) schemes for melamine in milk products and assigning reference values to the samples to provide participants with an independent benchmark to assess their accuracy. Melamine can be a challenging chemical to detect and quantify and tools such as matrix reference materials and PT schemes are essential in ensuring the quality of these measurements. Melamine continues to be a contaminant that is monitored in an ongoing way by the food industry and CCQM’s activities have helped ensure there is an effective internationally recognized metrology infrastructure to support this.

- **Supporting use of alternatives to natural gas.** As worldwide natural gas resources are declining, there is a growing interest in exploiting alternatives to the use of conventional natural gas. Examples include biogas, biomethane and liquefied biogas (LBG). These gases need to be accurately analysed for their content, in order for them to be injected into the national gas grid, both to calculate energetic value and avoid impurities that would affect appliances. CCQM-K112 addressed Biogas, a natural gas substitute. Biogas is very rich in carbon dioxide and nitrogen, and usually contains 0.3 % -- 0.6 % oxygen and approximately 1 % hydrogen. The results of the key comparison underlined the challenges with measuring the amount-of-substance fraction oxygen in energy gases, and will lead to better methods and standards for their characterization.

- **Supporting the development of next-generation solar cells.** In CCQM-K129, NMIs demonstrated the accuracy of surface analysis methods based on total number counting methodology to accurately characterise new generation multi-element alloy films. The film studied, Cu(In,Ga)Se2 (CIGS), is a promising material for next-generation solar cells. Recently, a power conversion efficiency of 22.6% was achieved using CIGS based solar cells. The market size of thin film solar cells is anticipated to hit USD 30 billion by 2024. However, the analysis of CIGS film is very difficult because it is a multi-element alloy film with non-uniform in-depth distribution of the constituents. The calibration and measurement capabilities developed at NMIs and proved by the Key Comparison can now be implemented for thin film analysis of a variety of multi-element alloy films used in various advanced industries.

- **Supporting the SI unit redefinitions and accurate measurements of the Avogadro constant.** The Avogadro constant $N_A$ was determined from measurements of the mass, volume, crystal lattice parameter and molar mass of a silicon sphere. A key requirement
for the molar mass determination is measuring the absolute isotopic composition of the silicon. The molar mass is calculated by multiplying the amount-of-substance fractions by the relative atomic masses of the three naturally occurring silicon isotopes ($^{28}\text{Si}$, $^{29}\text{Si}$, $^{30}\text{Si}$). The Si isotopic measurements have presented a demanding experimental challenge. CCQM-P160 has facilitated a collaborative investigation of the silicon isotope ratio measurements, including: selection of an optimum solvent for dissolution of the silicon and for the ICP-MS measurements; the enormous disparity in amount between $^{28}\text{Si}$ and the other two isotopes; overcoming instrumental interferences when determining the very low levels of $^{28}\text{Si}$ and $^{30}\text{Si}$; correcting for instrumental mass bias (K-factor calibration) between the three isotopes; methodology for processing the ICP-MS data to achieve a relative uncertainty of the molar mass of the silicon crystal of less than $1 \times 10^{-8}$. The outcomes of this work have been incorporated into the most recent measurements of the Avogadro constant.

4.3. Improving the state of the art of measurement science

The CCQM continues to provide a forum for exchange of information on technical activities. In the last five year period the CCQM WGs have organized sixteen workshops with the goal of exchanging information on research and development activities in chemical and biological measurement science and standards being undertaken by NMIs across a range of sectors. In addition, research and development activities have been stimulated by comparisons either in the preparation phase, frequently by the coordinating laboratory in developing and characterizing appropriate samples to demonstrate the compatibility of measurement capabilities or subsequent to comparisons where methods and capabilities have been developed to reduce measurement uncertainties. The CCQM 2017-2026 strategy document list twenty five publications in peer-reviewed journals that were stimulated or resulted from twenty one CCQM comparisons.

4.4. Redefinition of the SI units

The CCQM activities related to the redefinition of the SI units, have been led by the CCQM ad hoc WG on the mole, that has drafted a mise-en-pratique for the mole. Engagement and consultation with the chemical community has continued. A symposium on the mole was held as part of the ACS meeting in Boston in August 2015, in order to further publicise the changes being proposed. Strong liaison with IUPAC has continued throughout the period. The IUPAC Technical Report on “A critical review of the proposed definitions of fundamental chemical quantities and their impact on chemical communities (IUPAC Technical Report)”, Pure Appl. Chem. 89(7), pp. 951-981 (2017), https://doi.org/10.1515/pac-2016-0808 was published in 2017. The Technical Report presents an overall positive appreciation of the redefinition of the mole, based on a specified number of entities (typically atoms or molecules) that will not depend on the unit of mass, the kilogram. Proposals on the exact wording of the redefinition have been submitted by IUPAC to the CCQM, which has incorporated these in its recommendation to the CCU, and are also summarised in the publication “Definition of the mole (IUPAC Recommendation 2017)”’, Pure Appl. Chem. 90(1), pp. 175-180 (2018), https://doi.org/10.1515/pac-2017-0106. The activities of CCQM, including the extended consultation with the international chemical community, are expected to lead to a definition of the mole, and by consequence the quantity of amount of substance, that will be better understood by the scientific community at large, whilst ensuring that the accuracy of chemical measurements are maintained and no step function change in measurement will occur as a result of redefinition.
5. **Outlook in the short and long term**

The recently updated CCQM strategy document provides a comprehensive plan of activities for the CCQM in the near and longer term. The recommendation of the CIPM MRA review have been addressed in the strategy document, and the concept of broad claim CMCs is being slowly implemented. The evolution of the total number of CMCs will need continued surveillance, with stabilisation expected if the percentage coverage of NMI services covered by CMCs becomes the key performance indicator.

**Annex: CC Data**

**CCQM** set up in 1993  
President: W. E. May  
Executive secretary: R. I. Wielgosz  
Membership: 24 members, 6 liaisons and 11 observers


Meetings since the 24th CGPM meeting: 20-21 April 2015, 21-22 April 2016, 27-28 April 2017, 19-20 April 2018

[https://www.bipm.org/en/committees/cc/ccqm/working-groups.html](https://www.bipm.org/en/committees/cc/ccqm/working-groups.html)

11 Working Groups:  
Cell Analysis (CCQM-CAWG)  
Electrochemical and Classical Methods Analysis (CCQM-EAWG)  
Gas Analysis (CCQM-GAWG)  
Inorganic Analysis (CCQM-IAWG)  
Isotope Ratios (CCQM-IRWG)  
Key Comparisons and CMC Quality (CCQM-KCWG)  
Nucleic Acid Analysis (CCQM-NAWG)  
Organic Analysis (CCQM-OAWG)  
Protein Analysis (CCQM-PAWG)  
Surface Analysis (CCQM-SAWG)  
Strategic Planning Working Group (CCQM-SPWG)

1 *ad-hoc* Working Group:  
Working group on the mole

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<thead>
<tr>
<th><strong>CCQM Comparison activity</strong></th>
<th>Completed/ In progress</th>
<th>Planned</th>
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<tbody>
<tr>
<td>CCQM key comparisons</td>
<td>172</td>
<td>12 per year</td>
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<tr>
<td>BIPM on-going comparisons</td>
<td>1</td>
<td>1</td>
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<tr>
<td>CC pilot studies (stand-alone)</td>
<td>134</td>
<td>4 to 5 per year</td>
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<tr>
<td>CMCs</td>
<td>6412 CMCs in 67 service categories registered in the KCDB</td>
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