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

Dr. Willie E. May
President, CCQM
Vice President, CIPM
24rd Meeting of the CCQM Plenary, April 2018

70 Participants from: 24 member, 6 liaison and 11 observer organizations
Consultative Committee for Metrology in Chemistry and Biology (CCQM)

- Established by the CIPM in 1993
- 41 Member/Official Observer Organizations
- 11 Standing and 1 *ad hoc* Working Groups
  - In 2018 staffed by ~240 experts from NMI’s/DI’s
- Yearly meetings of CCQM plenary, attended by ~70 representatives from Member and Observer Institutes, stakeholder organizations, and guests

**Figures of Merit**

- ~6400 CMCs published in the KCDB for Chem/Bio measurement services
  - Number of analyte matrix combinations increasing at a rate of about 250 per year.
- 306 comparisons (172 Key and 134 Pilot) conducted or in progress
A Context for the Importance and Complexity of Chemical Measurements

- According to a study released by the Council for U.S. Chemical Research, chemistry is core or important to virtually all industrial sectors and technology areas

- For metrology in chemistry the task is to determine the quantity of a specific chemical entity in a given matrix and not merely "amount of substance" (i.e., requires confirmation of identify as well as amount)

- Chemical measurements are multidimensional
  - a large number of chemical entities (>10^5)
  - in a broad range of matrices (10^7)
  - and mass fractions ranging from <10^{-12} to 1
The Questions are Different for.... Measurements:

**Physical:** What’s the mass of Willie? 90 kg; What is Willie’s blood pressure, etc.

**Chemical:** How much cholesterol is there in Willie’s blood? 150 mg/dL

**Biological:** Which cholesterol-lowering drug would be best for Willie in terms of both efficacy and potential side effects? .... **Personalized Medicine**

Life processes are very complex and the information space is very vast

Krebs Cycle

Not as simple as we once thought
The CCQM is responsible for developing, improving and documenting the equivalence of national standards (certified reference materials and reference measurement procedures) for chemistry and biology.

It advises the CIPM on matters related to chemical and biological measurements including advice on the scope of BIPM’s scientific programme activities.
CCQM - Objectives

- to document and improve the global comparability of chemical and biological measurements
- to progress the state of the art of chemical and biological measurement science
- provide chem/bio metrology-related solutions to address important global/societal issues

While reaching out and getting input from stakeholders
From the 25th Meeting of the CGPM

Issues

• Exponential increase in interest/ needs for Comparisons and studies
• Steady Increase in number of CMCs to review
  – Continuing with the current approach at the same level of effort is not sustainable !!!
• Organizational Structure

Planned Actions

• Establishing a Strategic Planning Framework for Key Comparisons
  – defining a finite number of comparisons that test not the techniques -- but rather the institutional knowledge and core competencies required to deliver services recognized under CIPM MRA
• Examining basis and structure for CMCs
• Combining Inorganic and Electrochemical WGs; subdividing Bio WG
Managing the growth in CMCs and KC needs

CCQM (2017-2026) Strategy takes into account our own thinking + CIPM-MRA review outcomes:

- Transitioning to Broader Claim CMCs
- Strategic Planning Framework developed and instituted to identify a finite number of comparisons to test and document the institutional knowledge and core competencies that NMIs maintain to deliver their measurement services to customer

- **Outcome:** Growth in number of Chem-Bio CMCs has stabilised and even started to reduce

Evolution of Chemistry/Biology CMCs 2008-2018
Increased focus on measurement standards for Biology:

In 2015, CCQM Working groups on Nucleic Acids, Cellular and Protein Metrology were formed from the Bioanalysis WG

Subdivision of Biometrology Working Group

Cells

Nucleic Acids

Proteins
The responsibilities of the NAWG are:

To carry out Key Comparisons and where necessary pilot studies, to critically evaluate and benchmark NMI/DI claimed competences for measurement standards and capabilities for nucleic acid analysis:

- Including, but not limited to, chromosomes, DNA, nucleotides, oligonucleotides, modified DNA (e.g. DNA methylation and other epigenetic modifications), mRNA, miRNA and other short non-coding RNAs) in a biological measurement context;

- NA measurement includes, but is not limited to, the identification and quantification of nucleic acids in complex matrices (such as those derived from plant, animal and microbial origins)
Protein Analysis Working Group (established 2015)

The responsibilities of the PAWG are:

• To carry out key comparisons and, when necessary, pilot studies to critically evaluate and benchmark NMI/DI competence for measurement capabilities and standards for proteins and peptides;

  o To identify and establish inter-laboratory studies to enable the global comparability of protein and peptide measurement results through reference measurement systems of the highest possible metrological order with traceability to the SI, where feasible, or to other internationally agreed units

  o To act as a forum for exchanging information and idea for promoting implementation of metrology in protein/peptide measurement and will create opportunities for collaborations among stakeholders
Cell Analysis Working Group (established 2015)

The responsibilities of the CAWG are:

1) **To carry out Key Comparisons and pilot studies, to critically evaluate and benchmark NMI/DI competences for measurement capabilities and standards including, but is not limited to the identification and quantification of cells and cell properties indicative of function as a result of emergent behavior in complex matrices and mixtures.**

2) **To identify and establish inter-laboratory work and pilot studies to enable global comparability of cell analytical measurement results through reference measurement systems of the highest possible metrological order with traceability to the SI, where appropriate and feasible, or to other internationally agreed units, in response to the demands of NMI customers.**
## CCQM - Organizational Structure

**President:** W.E. May, CIPM  
**Executive Secretary:** R. Wielgosz, BIPM

### 11 Permanent Working Groups including 9 Technical Working Groups:

<table>
<thead>
<tr>
<th>Working Group</th>
<th>Chair</th>
<th>Deputy Chair</th>
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<tbody>
<tr>
<td>Organic Analysis (OAWG)</td>
<td>L. Mackay</td>
<td>K. Lippa</td>
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<td>Gas Analysis (GAWG)</td>
<td>J.S. Kim</td>
<td>P. Brewer</td>
</tr>
<tr>
<td>Inorganic Analysis (IAWG)</td>
<td>M. Sargent</td>
<td>P. Fisicaro</td>
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<tr>
<td>Classical Methods (CMWG)</td>
<td>M. Mariassy</td>
<td>S. Seltz</td>
</tr>
<tr>
<td>Surface Analysis (SAWG)</td>
<td>W. Unger</td>
<td>T. Fujimoto</td>
</tr>
<tr>
<td>Cellular Analysis (CAWG)</td>
<td>J. Morrow</td>
<td>NIST</td>
</tr>
<tr>
<td>Nucleic Acids Analysis (NAWG)</td>
<td>H. Parkes</td>
<td>LGC</td>
</tr>
<tr>
<td>Protein Analysis (PAWG)</td>
<td>S-R. Park</td>
<td>J. Melanson</td>
</tr>
<tr>
<td>Isotope Ratio Metrology (IRWG)</td>
<td>Z. Mester</td>
<td>NRC</td>
</tr>
<tr>
<td>Key Comparison and CMC Quality (KCWG)</td>
<td>W.M.(Della) Sin</td>
<td>GLHK</td>
</tr>
<tr>
<td>Strategic Planning (SPWG)</td>
<td>W. E. May</td>
<td>CIPM</td>
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### 1 Ad hoc Working Group and 1 Task Group:

- **Ad hoc working group on the mole**  
  Chair: B. Guettler  
  Deputy Chair: PTB

- **Task Group on Method Defined Measurands**  
  Chair: H. Andres  
  Deputy Chair: METAS
Addressing needs for accurate isotope ratio measurements

**Fundamental Science:**
- Atomic Weight determinations; often done by NMIs
- Avogadro Constant; silicon isotope ratio
- Boltzmann constant; argon isotope ratio
- Faraday constant; silver isotope ratio

**Realization of SI units**

**Trade & Commerce:**
- Provenance of:
  - food, e.g. $^{87}\text{Sr}/^{86}\text{Sr}$
  - commodities;
- Product authenticity; counterfeit pharma

**Environment:**
- Identifying and quantifying sources and sinks of GHGs;
- Prehistoric $\text{CO}_2$ records; boron-11
Comparisons on Grand Challenge Areas

- Health
- Energy & Environment
- Food Safety
- Advanced Manufacturing
Comparisons Selected Through Dialogue With Stakeholder Community

Continued interaction and workshops with stakeholder communities
### Harmonized Terminology for CCQM Comparisons

<table>
<thead>
<tr>
<th>Nomenclature for Comparison Type</th>
<th>Description</th>
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<tr>
<td><strong>Core key comparisons</strong></td>
<td>Demonstrates core measurement capabilities. All with claimed capabilities participate</td>
</tr>
<tr>
<td><strong>Specialized Key Comparisons</strong></td>
<td>Demonstrates capabilities in a narrow but Nationally or Regionally-relevant area. Participation voluntary</td>
</tr>
<tr>
<td><strong>Pilot Studies</strong></td>
<td>Learning exercises to examining particular measurement areas or techniques</td>
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Core Key Comparison – Purity Assessment

CCQM-K55.d: Mass fraction of Folic Acid

Degrees of equivalence, $D_j$ and expanded uncertainty $U_j (k = 2)$

$x_0 = 906.5$ mg/g
$U_x = 8.8$ mg/g

Methods
- Mass Balance
- QNMR
Core Key Comparison

CCQM-K120: CO₂ in air 380 µmol/mol to 800 µmol/mol

WMO-GAW Data Quality objective = ± 0.1 µmol/mol
Comparisons of NMI Measurement Capabilities and of Measurement Services “as delivered”

Documented degree of equivalence of measurement services “as delivered”

(Comparison of value-assignments of NMI/DI CRMs for Creatinine in Serum)
Specialized Key Comparisons

CCQM-K103: Melamine in milk powder: facilitating the safety testing of food products related to an internationally important food contamination issue
Vitamin D in Human Serum Measurements

- Vitamin D is an important steroid hormone.
- Concerns about the variability in clinical test results.
Accurate cell counting for patient treatment

Cell Counting for Bone Marrow Transplants Post Chemotherapy

CCQM-P165: CD34+ Cell Counting contributed to an international reference standard and value assignment for haematopoietic stem cells.
SI Traceable Reference Measurement Systems for Cancer and Infectious Disease Molecular Diagnostics

- Demonstration of world leading expertise in nucleic acid copy enumeration by digital PCR as a reference method through CCQM NAWG comparisons
- Established feasibility metrological traceability (to unit 1) for nucleic acid copy enumeration
- Clarification included in 9th SI brochure
- Significant stakeholder engagement & influence on technology manufacturers
Advanced Manufacturing: Standards for the International Technology Roadmap for Semiconductors

CCQM-K157 demonstrated the compatibility of HfO$_2$ thin film amount of substance measurements

Moore's law: The number of transistors in a dense integrated circuit doubles about every two years.

Gate dielectric thickness is limiting progress, with requirements below 2 nm, and will require replacing the silicon dioxide gate dielectric with a high-κ material (HfO$_2$)
Classical to Quantum SI

20 May 2019 – World Metrology Day

• Quantum SI
  – Quantum phenomena
  – Fundamental constants

• Tying metrology back to fundamental physics where possible

• kilogram
  – Planck constant

• kelvin
  – Boltzmann constant

• ampere
  – Elementary electric charge

• mole
  – Avogadro constant
Amount of Substance and the mole

Amount of Substance and the mole, are a useful quantity and unit to describe chemical behaviour at the macroscopic level

From IUPAC and CCU documents (circa 1971):

1. Chemists expressed the need for a quantity which was defined as directly proportional to the number of entities in a sample of a substance

2. It was preferable to adopt a convention with amount of substance having its own dimension. This convention was in wide use by Chemists and already recommended by IUPAC, IUPAP and ISO

3. The wish for chemists to adopt the SI – but the need to incorporate a base unit for amount of substance into the SI to make this happen
CCQM comparison for molar mass of 28Si determinations

CCQM-P160
(NIM, NRC, NMIJ, NIST, LGC, KRISS)
Avogadro's constant via Bragg's relationship

\[ N_{Si} = \frac{V_{\text{Sphere}}}{V_{\text{Atom}}} \]

\[ n_{Si} = \frac{N_{Si}}{N_A} = \frac{M_{Si}}{M(Si)} \]

\[ N_A = \left( \frac{M(Si)}{M_{Si}} \right) \left( \frac{V_{\text{Sphere}}}{V_{\text{Atom}}} \right) \]

\[ N_A = \frac{8 \cdot M(Si) \cdot V_{\text{sphere}}}{M_{Si} \cdot a^3} \]

\[ N_A h = \frac{cA_r(e)M_u \alpha^2}{2R_\infty} \]


see J. Stenger & E.O. Göbel, Metrologia 49 (2012), L25–L27
Consultation with the Community

CCQM has led an extensive consultation process with the international chemical community to ensure their requirements are met with the redefinitions, including:

- CCQM Workshop "The Redefinition of the Mole - A new era for chemical metrology?“ (2012)
- CCQM Workshop on the redefinition and realization of the mole (2014)
- CCQM Workshop at ACS Meeting, Boston USA, ‘Redefinition of the SI’ (2015)
- Support and Consultation on the IUPAC Project: ‘A critical review of the proposed definitions of fundamental chemical quantities and their impact on chemical communities’

Outcome:
Agreement on wording of redefinition between IUPAC, CCQM and CCU
Current definition of the mole

1. The mole is the amount of substance of a system which contains as many elementary entities as there are atoms in 0.012 kilogram of carbon 12; its symbol is "mol".

2. When the mole is used, the elementary entities must be specified and may be atoms, molecules, ions, electrons, other particles, or specified groups of such particles.

14th CGPM (1971, Resolution 3)

It follows that:

the \textbf{molar mass of carbon 12 is exactly 12 grams per mole, } M^{(12C)} = 12 \text{ g/mol}. 

In this definition, it is understood that unbound atoms of carbon 12, at rest and in their ground state, are referred to.

CIPM (1980)
Revised definition of the mole

The mole, symbol mol, is the SI unit of amount of substance.

One mole contains exactly $6.022\,140\,76 \times 10^{23}$ elementary entities.

This number is the fixed numerical value of the Avogadro constant, $N_A$, when expressed in the unit mol$^{-1}$ and is called the Avogadro number.

The amount of substance, symbol $n$, of a system is a measure of the number of specified elementary entities. An elementary entity may be an atom, a molecule, an ion, an electron, any other particle or specified group of particles.

*This draft definition of the mole for the new SI based on a specified number of elementary entities is more understandable, teachable and understandable by the chemical community*
CCQM Activities have -- without question --

- enabled NMIs to identify “spikes” of excellence within the chem/bio world that have led to establishment of strategic collaborations for both research and standards development purposes

- Improved the quality of chemical and biological measurements within the worldwide NMI community
  - Which has led to better (more and higher quality) services for end user customers
Celebrating our 25th Anniversary 10-12 April 2019

25-years of the CCQM: Where We’ve Been and Where Should We Be Going?

• Planning for a 3-day Plenary
  o Special Session will include historical and future perspectives as well as usual WG reports, etc.
  o Workshop on Advances in Metrology in Chemistry and Biology
    o Presentations in Special Issue of Metrologia
    o Young Metrologist and Best Poster Awards

Over 90 abstracts received
25 years of CCQM: April 2019

Advances in Metrology in Chemistry and Biology:

*Metrologia* ‘Focus on’ issue

Invited Review Papers and open call for research papers

**Focus issue papers**

**SI traceability and scales for underpinning atmospheric monitoring of greenhouse gases**
Paul J Brewer et al 2018 *Metrologia* **55** S174

- View abstract
- View article
- PDF

**A higher order method for the determination of total phosphorus in human serum**
Fransiska Dewi et al 2018 *Metrologia* **55** S195

- View abstract
- View article
- PDF
24th Meeting of the CCQM Plenary, April 2018

Thank you!

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