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

Dr. Willie E. May

President, CCQM

Vice President, CIPM

26e CGPM

Versailles

13-16 novembre 2018

Bureau International des Poids et Mesures

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 Obsever 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.

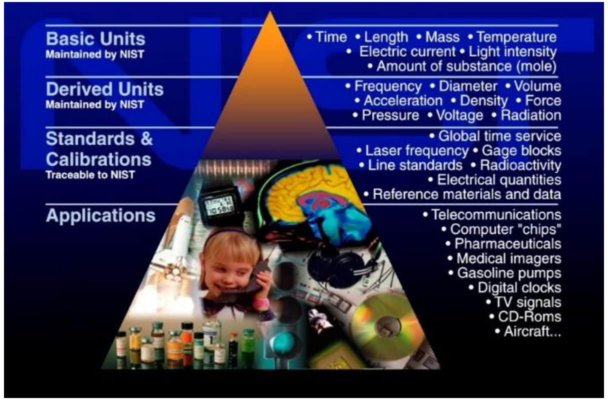
– **306 comparisons (172 Key and 134 Pilot) conducted or in progress**

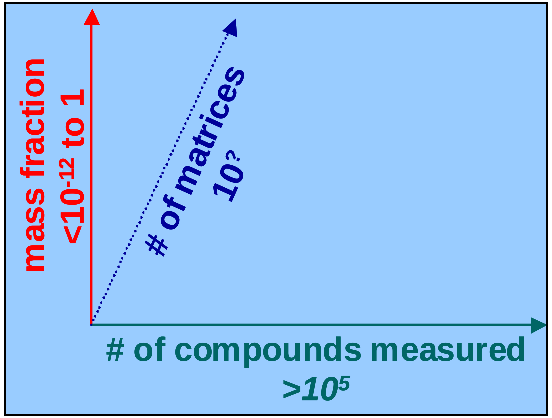
A Context for the Importance and Complexity of Chemical Measurements

- **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**
  - *"Measuring Up: Chemical R&D Counts for Everyone", CCR, 2006*

- **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 ($10^?$)
  - and mass fractions ranging from <10^{-12} to 1





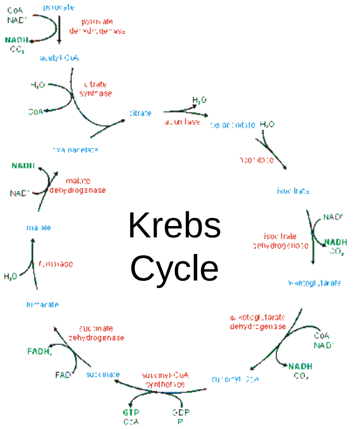
The Questions are Different for…. Measurements:

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

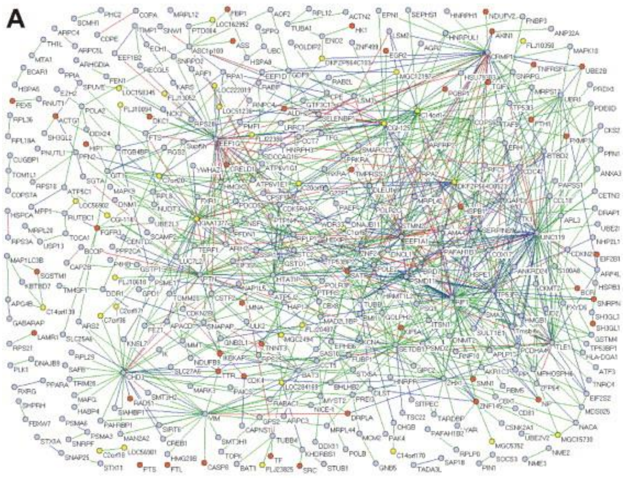
Chemical: How much cholesterol is there in Willie's blood? **150 mg/dL**

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



Not as simple as we once thought



CCQM - Terms of Reference

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 to 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

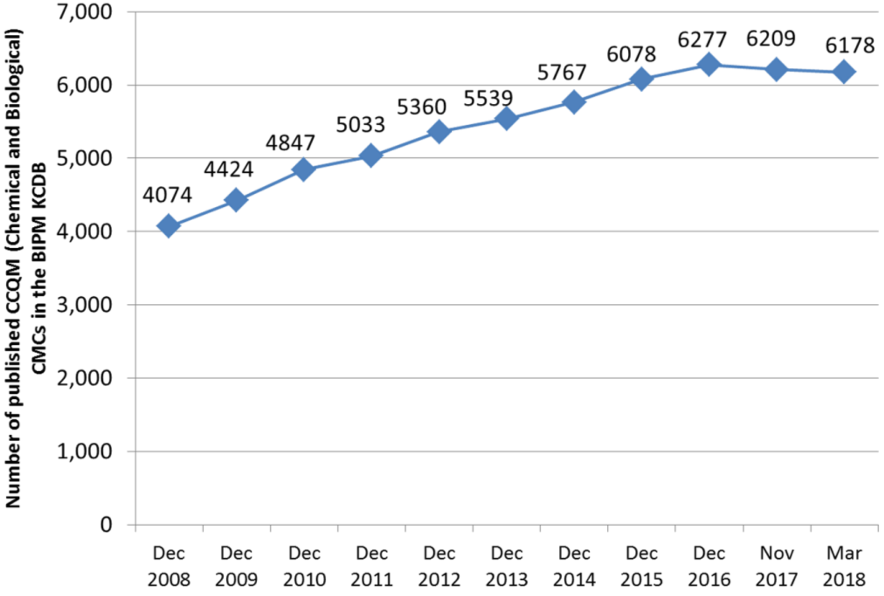
- Establishing a Strategic Planning Framework for Key Comparisons
  - defining a finite number of comparisons that test not the techniques -- but rather the institutional knowledge and core competencies required to deliver services recognized under CIPM MRA
- Examining basis and structure for CMCs
- 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

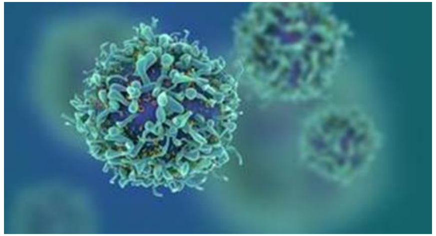


Evolution of Chemistry/Biology CMCs 2008-2018

Subdivision of Biometrology Working Group

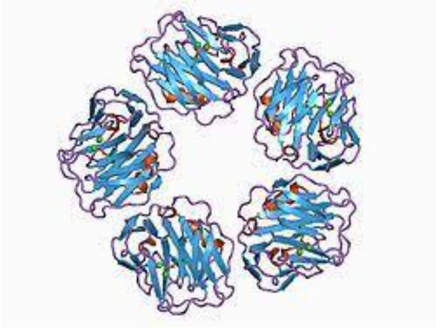
Increased focus on measurement standards for Biology:

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



Cells

Nucleic Acids



Proteins

Nucleic Acid Analysis Working Group (established 2015)

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;**

    - 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

    - 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:

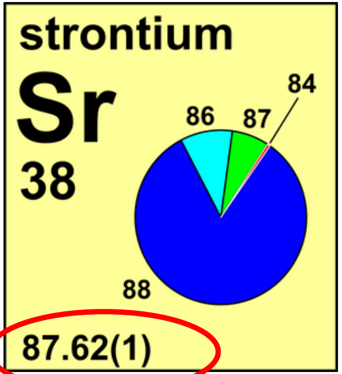
Working Group	WG Chair		Deputy Chair	
– Organic Analysis (OAWG)	L. Mackay	NMIA	K. Lippa	NIST
– Gas Analysis (GAWG)	J.S. Kim	KRISS	P. Brewer	NPL
– Inorganic Analysis (IAWG)	M. Sargent	LGC	P. Fisicaro	LNE
– Classical Methods (CMWG)	M. Mariassy	SMU	S. Seltz	PTB
– Surface Analysis (SAWG)	W. Unger	BAM	T. Fujimoto	NMIJ
– Cellular Analysis (CAWG)	J. Morrow	NIST		
– Nucleic Acids Analysis(NAWG)	H. Parkes	LGC		
– Protein Analysis (PAWG)	S-R. Park	KRISS	J. Melanson, NRC	
– Isotope Ratio Metrology (IRWG)	Z. Mester	NRC		
– Key Comparison and CMC Quality (KCWG)	W.M.(Della) Sin	GLHK	A. Botha	NMISA
– Strategic Planning (SPWG)	W. E. May	CIPM		

***1 Ad hoc* Working Group and 1 Task Group:**

– *ad hoc* working group on the mole	B. Guettler	PTB
– *Task Group on Method Defined Measurands*	H. Andres	METAS

Addressing needs for accurate isotope ratio measurements

source: http://www.ciaaw.org/mercury.htm



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

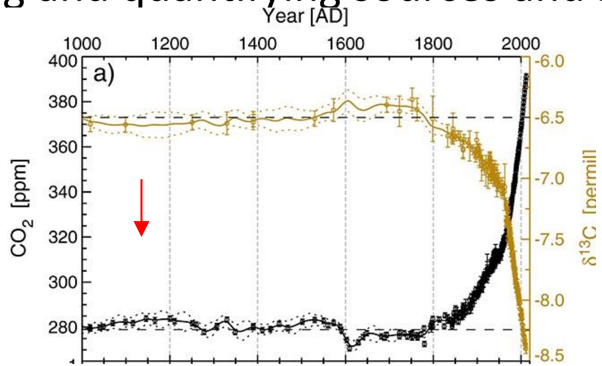
Trade & Commerce:

- Provenance of:
  - food, e.g. $^{87}Sr/^{86}Sr$
  - commodities;
- Product authenticity; counterfeit pharma

Adapted from: http://www.sxc.hu/photo/488070

Environment:

- Identifying and quantifying sources and sinks of GHGs;



- Prehistoric CO_2 records; boron-11

Adapted from DOI: (10.1002/jgrd.50668)

Comparisons on Grand Challenge Areas

- Health
- Energy & Environment
- Food Safety
- Advanced Manufacturing

Comparisons Selected Through Dialogue With Stakeholder Community

WORLD ANTI-DOPING AGENCY

IUPAC
INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY

UNITS
2012, 2014, 2017

ANTI-DOPING ANALYSIS
2016

AIR QUALITY
2007, 2010

WMO

ENFSI

FORENSICS
2010

SI
kg m s A K mol cd

GREENHOUSE GASES
2015

IAEA.org
International Atomic Energy Agency

FOOD ANALYSIS
2005

PHARMA
2008

USP
U.S. Pharmacopeial Convention

MICROBIOLOGY
2011

IVD
2002,2005, 2009

Food and Agriculture Organization of the United Nations

World Health Organization

ifcc
International Federation of Clinical Chemistry and Laboratory Medicine

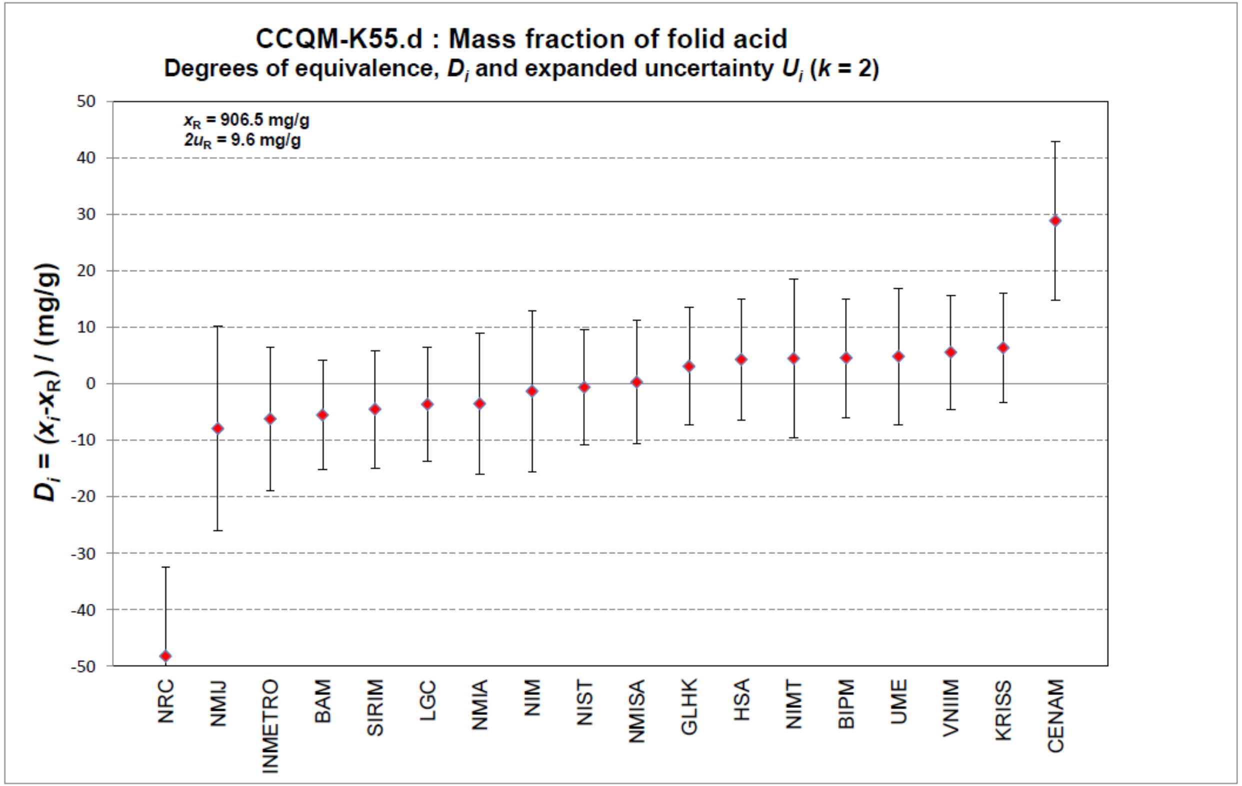
edqm
European Directorate for the Quality of Medicines & HealthCare

Continued interaction and workshops with stakeholder communities

Harmonized Terminology for CCQM Comparisons

Nomenclature for Comparison Type	Description
Core key comparisons	Demonstrates core measurement capabilities. All with claimed capabilities participate
Specialized Key Comparisons	Demonstrates capabilities in a narrow but Nationally or Regionally- relevant area. Participation voluntary
Pilot Studies	Learning exercises to examining particular measurement areas or techniques

Core Key Comparison – Purity Assessment

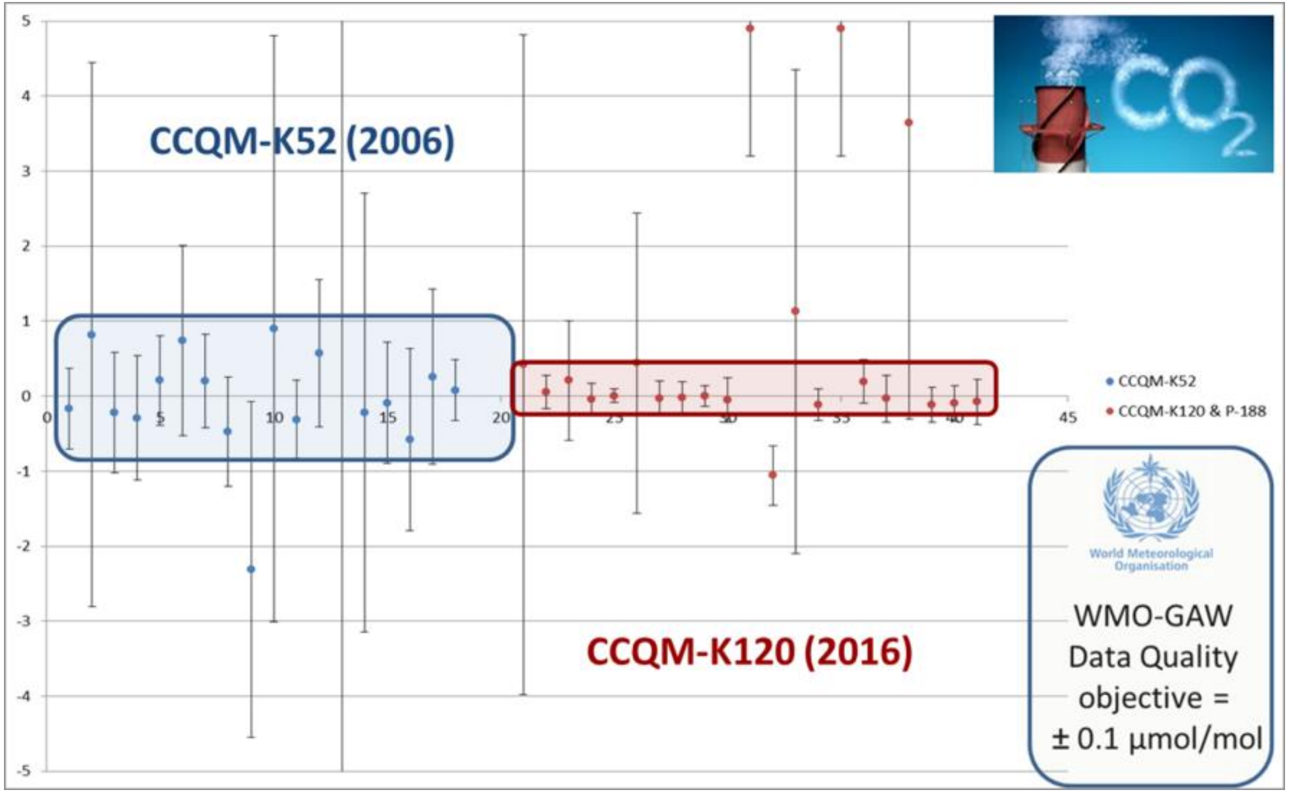


CCQM-K55.d Mass fraction of Folic Acid

Methods

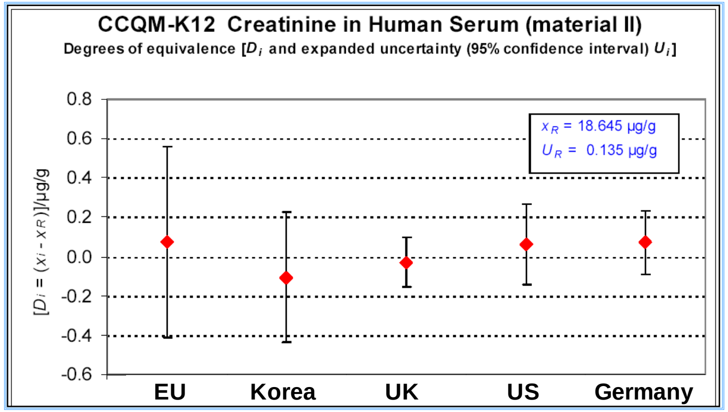
- Mass Balance
- QNMR

Core Key Comparison



CCQM-K120:
CO_2 in air
380 µmol/mol to 800 µmol/mol

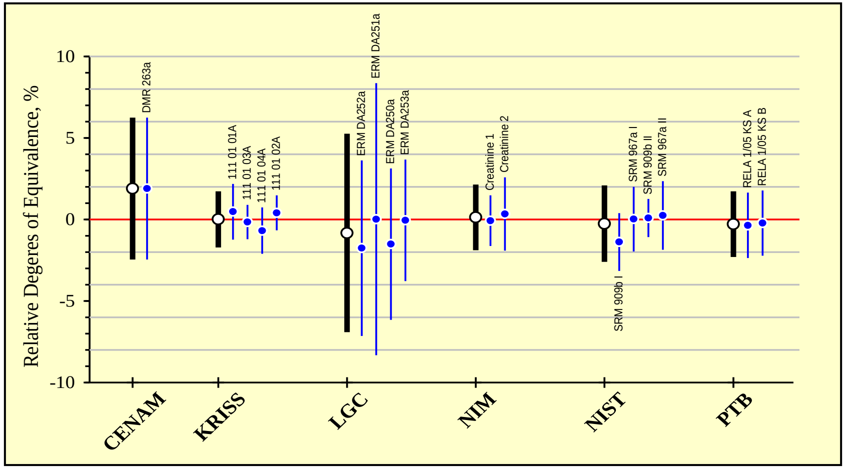
Comparisons of NMI Measurement Capabilities and of Measurement Services “as delivered”



Documentation of capabilities maintained by NMIs/DI’s to deliver services

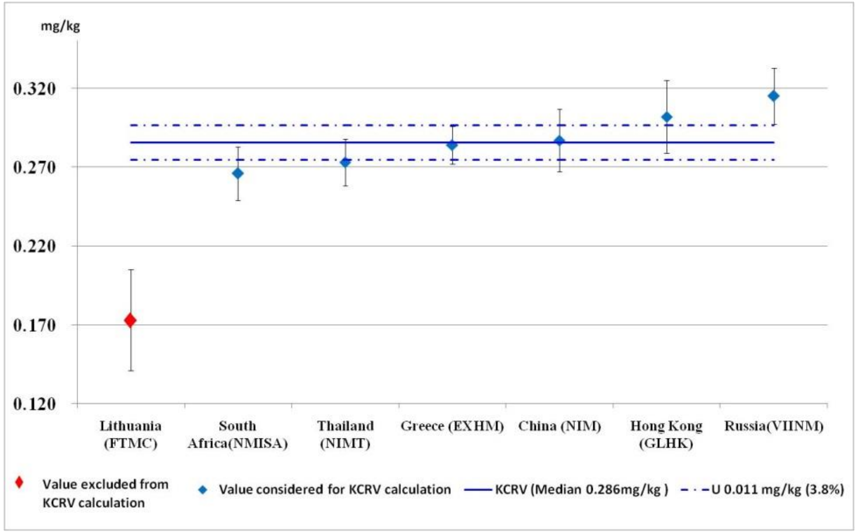
Documented degree of equivalence of measurement services “as delivered”
(Comparison of value-assignments of NMI/DI CRMs for Creatinine in Serum)

CCQM-K80



Specialized Key Comparisons

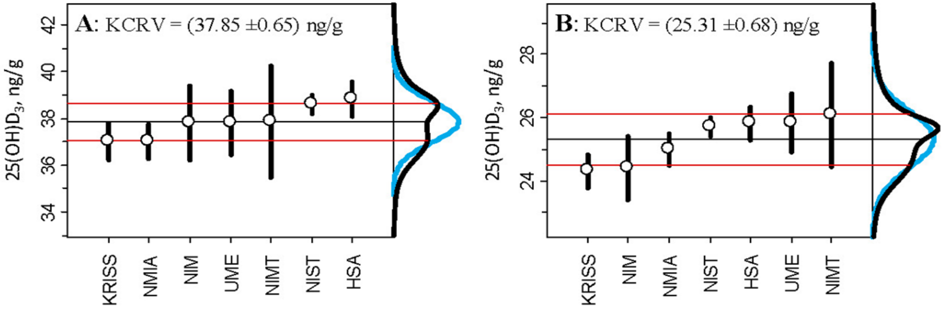
CCQM-K103: Melamine in milk powder: facilitating the safety testing of food products related to an internationally important food contamination issue



Vitamin D in Human Serum Measurements

- Vitamin D is an important steroid hormone.
- Concerns about the variability in clinical test results.

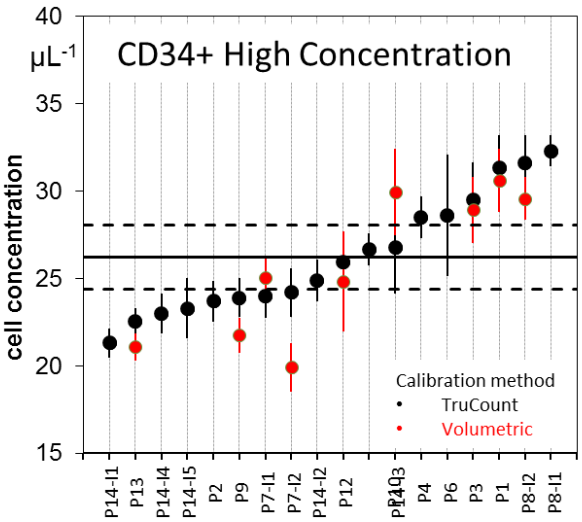
CCQM-K132 Vitamin D in Serum

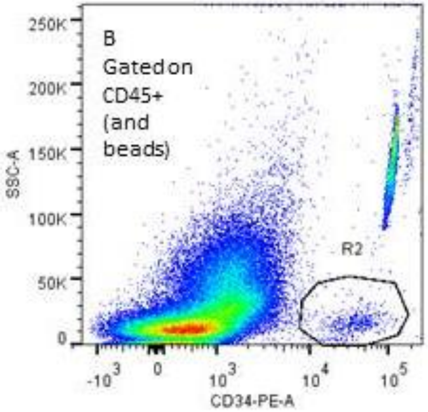


Accurate cell counting for patient treatment

Cell Counting for Bone Marrow Transplants Post Chemotherapy

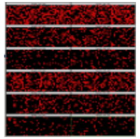
CCQM-P165: CD34+ Cell Counting contributed to an international reference standard and value assignment for haematopoietic stem cells.

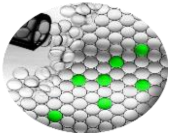




PTB Physikalisch-Technische Bundesanstalt Braunschweig und Berlin
LGC
KRISS
NIST National Institute of Standards and Techn U.S. Department of Comr
INRiM ISTITUTO NAZIONALE DI RICERCA METROLOGICA
NIBSC Confidence in Biological Medicines
TÜBİTAK UME
INMETRO
中国计量科学研究院 National Institute of Metrology,China

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

www.bipm.org

analytical chemistry

Article

An International Comparison of Enumeration-based Quantification of DNA Copy-concentration Using Flow Cytometric Counting and Digital Polymerase Chain Reaction

Heebong Yoo, Sang-Ryoul Park, Lianhua Dong, Jing Wang, Zhiwei Sui, Jernej Pavši#, Mojca Milavec, Muslum Akgoz, Erkan Mozio#lu, Philippe Corbisier, Janka Matrai, Bruno Cosme, Janaina Japiassu de Vasconcelos Cavalcante, Roberto Becht Flatshart, Daniel Gerard Burke, Michael Forbes-Smith, Jacob L. H. McLaughlin, Kerry R. Emslie, Alexandra S. Whale, Jim Francis Huggett, Helen Parkes, Margaret Kline, Jo Lynne Harenza, and Peter M Vallone

Anal. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.analchem.6b03076 • Publication Date (Web): 10 Nov 2016

There are also some quantities that cannot be described in terms of the seven base quantities of the SI, but have the nature of a count. Examples are a number of molecules, a number of cellular or biomolecular entities (for example copies of a particular nucleic acid sequence), or degeneracy in quantum mechanics. Counting quantities are also quantities with the associated unit one.

The unit one is the neutral element of any system of units – necessarily and present automatically. There is no requirement to introduce it formally by decision. Therefore, a formal traceability to the SI can be established through appropriate, validated measurement procedures.

Clinical Chemistry 64:9
1296–1307 (2018)

Special Report

Assessment of Digital PCR as a Primary Reference Measurement Procedure to Support Advances in Precision Medicine

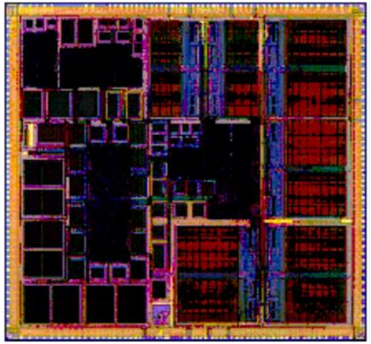
Alexandra S. Whale,[1†] Gerwyn M. Jones,[1†] Jernej Pavšič,[2,3] Tanja Dreo,[2] Nicholas Redshaw,[1] Sema Akyürek,[4] Müslüm Akgöz,[4] Carla Divieto,[5] Maria Paola Sassi,[5] Hua-Jun He,[6] Kenneth D. Cole,[6] Young-Kyung Bae,[7] Sang-Ryoul Park,[7] Liesbet Deprez,[8] Philippe Corbisier,[8] Sonia Garrigou,[9] Valérie Taly,[9] Raquel Larios,[10] Simon Cowen,[11] Denise M. O'Sullivan,[1] Claire A. Bushell,[1] Heidi Goenaga-Infante,[10] Carole A. Foy,[1] Alison J. Woolford,[1] Helen Parkes,[1] Jim F. Huggett,[1,12*†] and Alison S. Devonshire[1*†]

BACKGROUND: Genetic testing of tumor tissue and circulating cell-free DNA for somatic variants guides patient treatment of many cancers. Such measurements will be fundamental in the future support of precision medicine. However, there are currently no primary reference measurement procedures available for nucleic acid quantification that would support translation of tests for circulating tumor DNA into routine use.

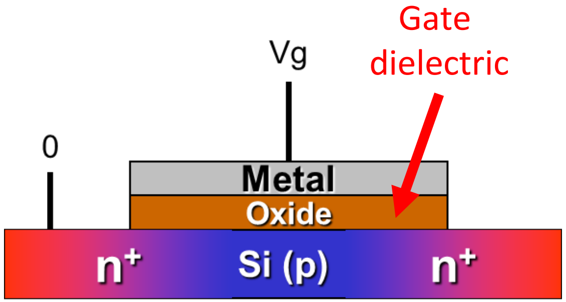
METHODS: We assessed the accuracy of digital PCR (dPCR)

CONCLUSIONS: This work validates dPCR as an SI-traceable reference measurement procedure based on enumeration and demonstrates how it can be applied for assignment of copy number concentration and fractional abundance values to DNA reference materials in an aqueous solution. High-accuracy measurements using dPCR will support the implementation and traceable standardization of molecular diagnostic procedures needed for advancements in precision medicine.

Advanced Manufacturing: Standards for the International Technology Roadmap for Semiconductors



CPU



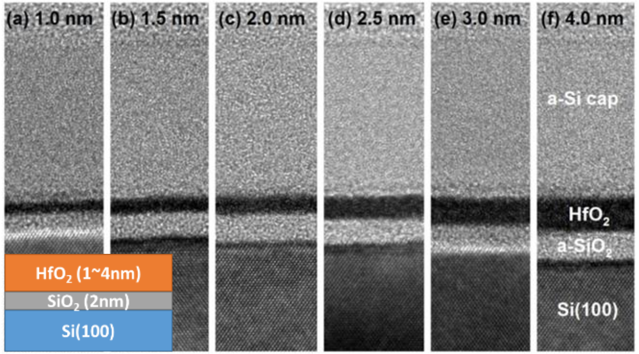
MOS-FET

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)

HfO_2 samples for CCQM K-157



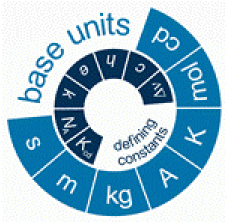
Classical to Quantum SI

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):

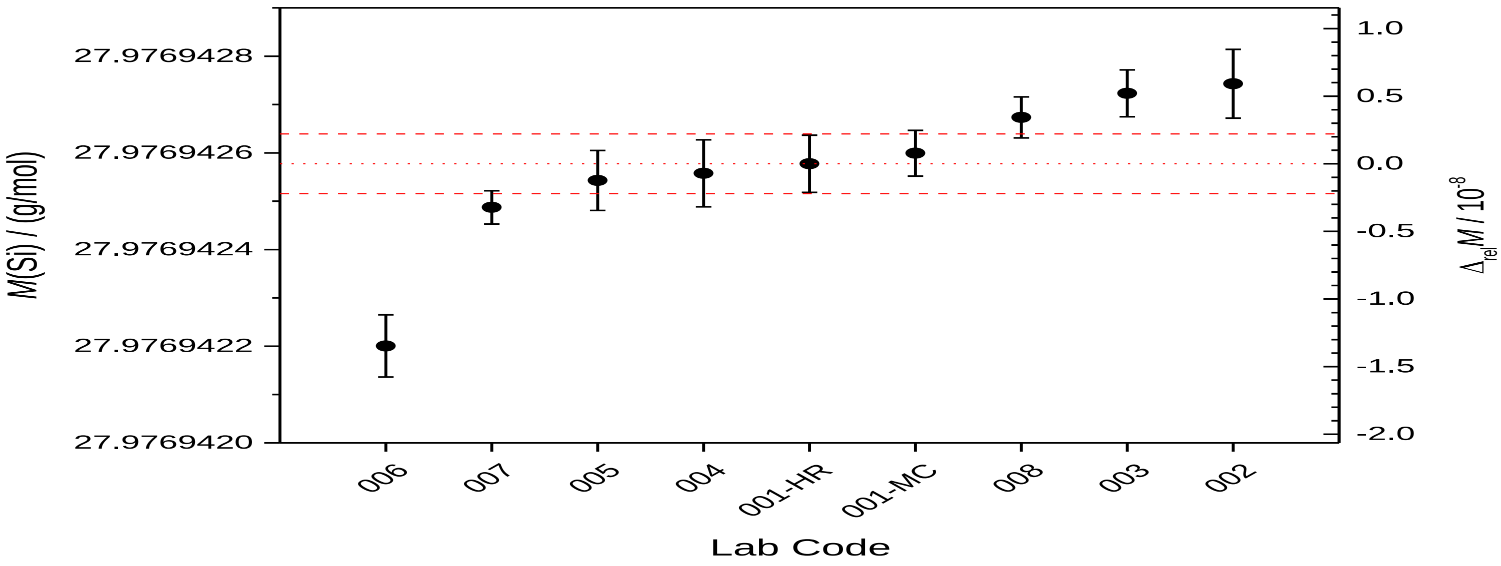
1. Chemists expressed the need for a quantity which was defined as directly proportional to the number of entities in a sample of a substance

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

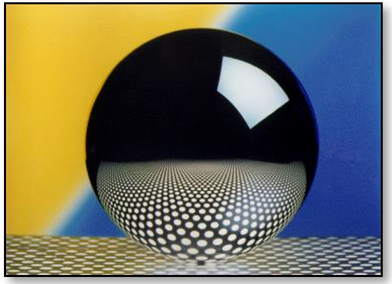
3. The wish for chemists to adopt the SI – but the need to incorporate a base unit for amount of substance into the SI to make this happen

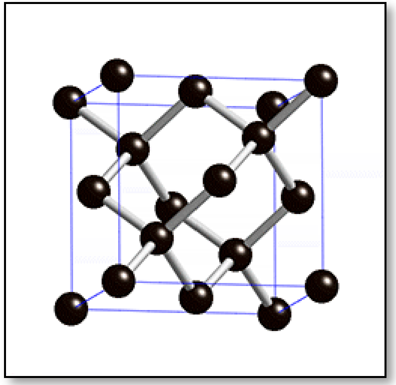
CCQM comparison for molar mass of 28Si determinations

CCQM-P160
(NIM, NRC, NMIJ, NIST, LGC, KRISS)



Avogadro's constant via Bragg's relationship





http://www.msm.cam.ac.uk/phase-trans/2003/MP1.crystals/MP1.crystals.html

$$N_{Si} = V_{\mathrm{Sphere}} / V_{\mathrm{Atom}}$$

$$n_{Si} = N_{Si}/N_{\mathrm{A}} = M_{Si}/M(Si)$$

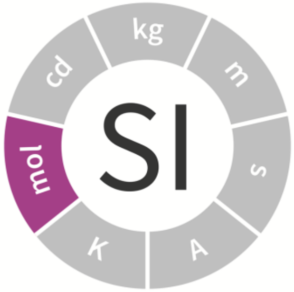
$$N_{\mathrm{A}} = (M(Si)/M_{Si})\,(V_{\mathrm{Sphere}} / V_{\mathrm{Atom}})$$

$$N_{\mathrm{A}} = \frac{8 \cdot M(Si) \cdot V_{\mathrm{sphere}}}{M_{Si} \cdot a^3}$$

$$N_A h = \frac{c A_r(e) M_u \alpha^2}{2 R_\infty}$$

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

Consultation with the Community



DE GRUYTER Pure Appl. Chem. 2018; 90(1): 175–180

IUPAC Recommendations

Roberto Marquardt, Juris Meija, Zoltán Mester, Marcy Towns, Ron Weir, Richard Davis and Jürgen Stohner*

Definition of the mole (IUPAC Recommendation 2017)

https://doi.org/10.1515/pac-2017-0106
Received January 11, 2017; accepted September 12, 2017

Abstract: In 2011 the General Conference on Weights and Measures (CGPM) noted the intention of the International Committee for Weights and Measures (CIPM) to revise the entire International System of Units (SI) by linking all seven base units to seven fundamental physical constants. Of particular interest to chemists, new definitions for the kilogram and the mole have been proposed. A recent IUPAC Technical Report discussed these new definitions in relation to immediate consequences for the chemical community. This IUPAC Recommendation on the preferred definition of the mole follows from this Technical Report. It supports a definition of the mole based on a specified number of elementary entities, in contrast to the present 1971 definition.

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 **molar mass of carbon 12 is exactly 12 grams per mole, $M(^{12}C) = 12$ 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.

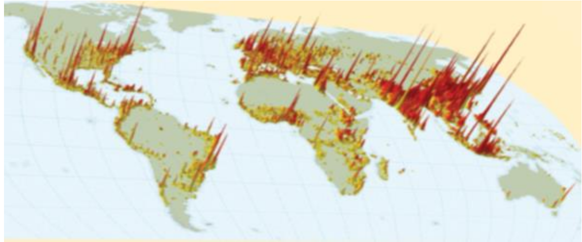
The amount of substance, symbol n, of a system is a measure of the number of specified elementary entities. An elementary entity may be an atom, a molecule, an ion, an electron, any other particle or specified group of particles.

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

A Global forum for
progressing the state-of-the art for Chemical and Biological Measurements

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?

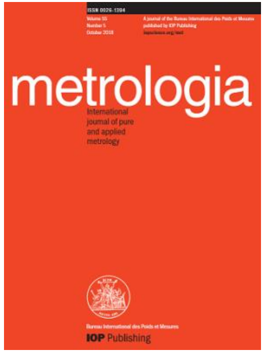
- Planning for a 3-day Plenary
  - Special Session will include historical and future perspectives as well as usual WG reports, etc.
  - Workshop on Advances in Metrology in Chemistry and Biology
    - Presentations in Special Issue of Metrologia
    - Young Metrologist and Best Poster Awards

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

26e CGPM

Versailles

13-16 novembre 2018

Thank you!

Bureau International des Poids et Mesures

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