CCQM Strategy Document for Rolling Programme Development

Date drafted: 23 May 2013 (Revised 30 January 2014)
Period covered: 2013-2023

1. General Information on CC Body (CC or a CC WG):

CC Name: **CCQM**
Date Established: **1993**
Number of Members: **27 members; 11 Observers**
Number of Working Groups: **10**
Number of Participants at last meeting: **65**
Periodicity between Meetings: **1 year**
Date of last meeting: **18-19 April 2013**
CC President: **Dr Willie E May, NIST, from 01/01/2013**
Number of KCs organized (from 1999 up to and including 2012): **113 Key comparisons (52 run with parallel pilot studies)**
Number of Pilot studies organized (from 1999 up to and including 2012): **115 additional pilot studies**
Number of CMCs published in KCDB supported by CC body activities (up to and including 2012): **5360**

2. Terms of Reference

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 advises the CIPM on matters related to chemical and biological measurements including advice on the BIPM scientific programme activities.

The responsibilities of the CCQM are:

a. to establish global comparability of measurement results through promoting traceability to the SI, and where traceability to the SI is not yet feasible, to other internationally agreed references;
b. to contribute to the establishment of a globally recognized system of national measurement standards, methods and facilities for chemical and biological measurements;
c. to contribute to the implementation and maintenance of the CIPM MRA with respect to chemical and biological measurements;
d. to review and advise the CIPM on the uncertainties of the BIPM's calibration and measurement services as published on the BIPM website;
e. to act 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.

In order to carry out its responsibilities, the CCQM has currently eight established working groups and two ad-hoc working groups. The established working groups (with the exception of the KCWG and the SPWG) all have the following common responsibilities:

a) to foster the establishment of global comparability of chemical and biological measurement results in their field of expertise by organizing comparisons and developing appropriate measurement methods and procedures in support of claimed capabilities and competences;
b) to provide input into the development of a CCQM strategic plan and develop and maintain a work plan consistent with the strategic plan adopted by the CCQM;

c) to evaluate new measurement technologies for their use in the value assignment of measurement standards
d) to interface with other CCQM WGs and international stakeholder organizations working on measurands covered by the working group;
e) to support the RMOs in the critical evaluation of calibration and measurement capabilities of NMIs to be entered into Appendix C of the CIPM-MRA.

In addition, working group specific responsibilities are listed below.

1) **Organic Analysis Working Group (OAWG) (established 1997)**
The responsibilities of the OAWG are:
(1) To carry out Key Comparisons, and where necessary pilot studies, to critically evaluate and benchmark NMI/DI claimed capabilities and competences for the execution of "higher order" measurement procedures for well-defined organic molecular entities for which the SI traceable amount of substance is to be determined ("Organic molecular entities" are taken to exclude gaseous compounds, organometallic compounds, and large bio-molecules).
(2) To consider, on a selective basis, similar activities for high-priority method-dependent analyses/measures.

2) **Gas Analysis Working Group (GAWG) (established 1997)**
The responsibilities of the GAWG are:
(1) To carry out Key Comparisons, and where necessary pilot studies, to critically evaluate and benchmark NMI/DI claimed competences for standards and capabilities for gas composition (including binary and multicomponent mixtures); gas/liquid mixture composition; nanoparticle and aerosol concentration; isotope ratio measurement; concentration of dissolved gases in liquid or solid matrices;
(2) To assist in identifying and establishing inter-laboratory work, pilot studies and research activities to provide SI traceable measurement results with reduced uncertainties for new measurement technologies in gas analysis such as dynamic dilution techniques for unstable gases, as well as spectroscopic techniques with the potential to be used as primary methods.

3) **Inorganic Analysis Working Group (IAWG) (established 1997)**
The responsibilities of the IAWG are:
(1) 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 the amount of substance fraction or mass fraction measurements of the elements; their isotopes and isotope ratios (absolute or relative); cations and anions; inorganic compounds; and organo-metallic compounds. Matrices to be covered include: pure materials, calibration solutions and complex samples such as those used for matrix reference materials.
(2) To assist in identifying and establishing inter-laboratory work and pilot studies for the purpose of jointly developing new methodology and investigating issues associated with SI traceability.

4) **Electrochemical Analysis Working Group (EAWG) (established 1998)**
The responsibilities of the EAWG are:
(1) 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 pH, electrolytic conductivity measurements and coulometry;
(2) To assist in identifying and establishing inter-laboratory work to improve the SI traceability of electrochemical measurement results.

5) **Key Comparison and CMC quality Working Group (KCWG) (established 2000)**
The terms of reference of the KCWG are described in the section 10 of the CIPM document "Calibration and Measurement Capabilities in the context of the MRA" (CIPM MRA-D-04). Within CCQM, the CCQM KCWG is responsible for overseeing the review of CMCs, defining specific technical review criteria, coordinating the inter-regional review process, providing guidance on the range of CMCs supported by specific comparisons, identifying where comparisons are needed and coordinating the review of existing CMCs in the context of new information.

6) **Bioanalysis Working Group (BAWG) (established 2002)**
The responsibilities of the BAWG are:
(1) 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 bioanalysis (bioanalysis covers large macromolecules and biomolecular entities – where the target species (analyte) is of biological origin (including, but not limited to, genes, proteins, cells) in a biological measurement context; biomeasurement includes, but is not limited to, the identification and quantification of macromolecules and cells in complex matrices and mixtures relevant for functional activity).
(2) To identify and establish inter-laboratory work and pilot studies to enable the global comparability of bioanalytical 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, in response to the demands of end users

7) **Surface Analysis Working Group (SAWG) (established 2004)**
The responsibilities of the SAWG are:
(1) 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 spatially resolved chemical surface analysis at the micro and nanoscale;
(2) To assist in identifying and establishing inter-laboratory work to improve the traceability of spatially resolved chemical surface analysis at the micro and nanoscale;

8) ***AD HOC* STEERING GROUP ON MICROBIAL MEASUREMENTS (MBSG) (established 2011)**
The responsibilities of the *ad hoc* MBSG are:
(1) to establish contacts and cooperation with the stakeholders/participants in the CCQM Workshop on Metrology and the Need for Traceable Microbiological Measurements to Ensure Food Quality and Safety, held on April 6-7, 2011 at the BIPM;
(2) to invite representatives from the stakeholders/participants and NMIs/DIs having activities in the field of food measurements and CRMs to join in the Steering Group;
(3) to investigate in close cooperation with the food community, two relevant but "simple" measurement cases, of which the measurand can be clearly defined and for which a metrologically sound validated method can become developed;
(4) to execute the two cases, including the organization of global comparisons, and reporting back to the CCQM and the microbial stakeholders/participants;
(5) to discuss and propose on the basis of the results what can be achieved, what should be planned and prioritized next, and how future cooperation can be best organized

9) ***Ad hoc* Working Group on the Mole (established 2007)**
The responsibilities of the *ad hoc* WG on the mole are:
(1) to draft a "mise-en-pratique" for the realization of the mole;
(2) to create awareness with respect to a possible redefinition of the mole, explain reasons and prepare opinions for discussion in the CCQM.

A draft "mise-en-pratique" has been produced, and is still under discussion.

10) ***Ad hoc* Working group on the Key Comparison Reference Value-KCRV (established in 2007; closed in 2013)**

The responsibilities of the KCRVWG are:

(1) to draft guidelines for the pragmatic and realistic application of statistical procedures when calculating measurement uncertainty in comparisons;

(2) to draft guidance for calculating a Key Comparison Reference Value

A number of guidance documents have been produced, discussed by the CCQM and presented to the CCQM Working Groups for further consideration.

The CCQM considered that the WG had completed its tasks and closed the WG at is 19th meeting in April 2013.

11) **Strategic Planning Working Group (SPWG) (established in 2012)**

The strategic planning working group is chaired by the CCQM President and its membership is composed of the CCQM WG Chairs, RMO Metrology in Chemistry Technical Committee Chairs and the CCQM Executive Secretary. The Strategic Planning Working Group was previously the *ad hoc* CCQM Advisory Group for the BIPM Programme in Metrology in Chemistry, which was first established in 2006.

The responsibilities of the SPWG are:

(1) to draft and update the CCQM Strategic Planning Document , with input from the CCQM WGs and RMO TCs in Metrology in Chemistry, for review, comment and approval by the CCQM;

(2) to develop and advisory opinion on the BIPM programme in Metrology in Chemistry for comment, review and approval by the CCQM.

3. Baseline (description status of activities and achievements up to and including 2012)

3.1 CCQM Achievements since 1999

At the end of the period 1999-2012, the NMIs participating in the CCQM have published **5360** calibration and measurement capabilities (CMCs) in the BIPM KCDB. In order to underpin these CMCs the CCQM has coordinated **113 Key comparisons** (52 of which were run with parallel pilot studies) and **115 separate pilot studies** over this period. The CCQM comparison programme has been supported since 2000 by the BIPM Chemistry Department comparison coordination activities, which have been formulated and prioritized with the advice of the CCQM. During this period the BIPM has coordinated **5 key comparisons** and **7 separate pilot studies**, with **263 NMI participations** in these comparisons. Figure 1 shows how the total number of published chemical and biological CMCs has evolved over the period 2000-2012.

The **5360** published CMCs in the database correspond to services covering **measurands for 830 different analytes, and 3049 different analyte-matrix combinations**.

Analyte refers to the component represented in the name of a measurable quantity, e.g. in "amount of substance of glucose in plasma", "glucose" is the analyte, whereas the entire phrase represents the **measurand**. The number of different analyte-matrix combinations is a good approximation to the different number of measurands covered by the published CMCs.

The information for each one of the 15 Chemical and Biological CMC categories is summarized in Table 1. The numbers of NMIs providing CMCs for a specific CMC category ranges from 2 (for materials not covered in the other 14 categories) and 6 (for Fuels) to 33 (for Gases) in December 2012. The median number of NMIs providing CMCs in a category is **16**, and the total number of NMIs/DIs providing Chemical and Biological CMCs is **50** from **39 different countries**. The number of

CMCs published up to December 2008 is also shown in Table 1. Over the last 4 years the number of CMCs has increased by an average of around **320 CMCs a year**, and the number of countries providing and publishing CMCs has increased from **30 to 39**. During the last 4 year period the CCQM has started its first re-review of existing CMCs, and in certain categories (pH and Metal and Metal Alloys) this has led to reductions in the total number of CMCs published.

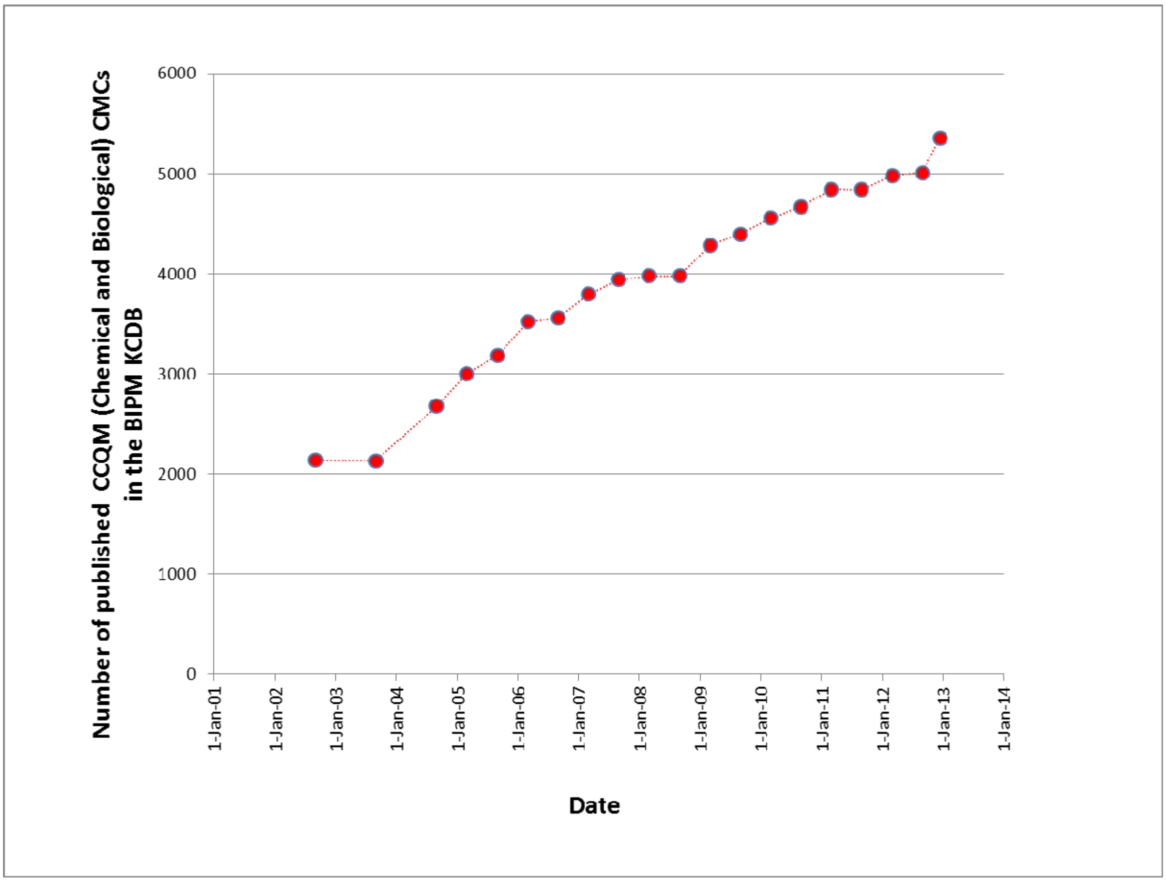

Figure 1. Evolution of the total number of published Chemical and Biological CMCs in the BIPM KCDB (2000-2012)

The development of reference measurement systems and CMCs for the Chemical and Biological fields has been driven by the increasing need for data of known quality for making decisions on high impact areas and sectors, such as Health, the Environment and Climate, Energy, Advanced Materials and the Food Safety.

As user needs for internationally equivalent and accurate measurements in various sectors have developed the CCQM has reacted by creating appropriate working groups to coordinate comparisons and studies to address these issues. Following the creation of four working groups in 1997/8 (covering Organic, Inorganic, Gas, and Electrochemical Analysis), working groups covering Bioanalysis (established 2002), Surface Analysis (established 2004) and an *ad hoc* Steering Group on Microbial Measurement (established 2011) have developed active programmes in coordinating key comparisons and studies to meet stakeholder needs. Examples of the impact of CCQM Comparisons and the calibration and measurement capabilities they support in a number of key sectors are given in Appendix II, and cover the areas of health care, environment and climate change, food safety, energy, advanced manufacturing, and the redefinition of SI units.

CMC Category	Number of CMCs per Category in Dec 2012	Number of analyte-matrix combinaisons in Dec 2012	Number of analytes in Dec 2012	Number of NMI service providers in Dec 2012	Number of CMCs per Category in Dec 2008	Change in number of CMCs per Category (Dec 2008 to Dec 2012)
1: High purity chemicals	445	404	388	16	263	182
2: Inorganic Solutions	361	219	101	15	324	37
3: Organic Solutions	473	322	254	16	351	122
4: Gases	2039	583	213	33	1500	539
5: Water	160	130	45	18	132	28
6: pH	79	1	1	19	89	-10
7: Electrolytic Conductivity	38	3	1	16	27	11
8: Metal and metal alloys	194	163	42	7	276	-82
9: Advanced materials	113	78	40	12	56	57
10: Biological fluids and materials	382	324	164	16	316	66
11: Food	426	384	161	20	241	185
12: Fuels	54	49	29	6	47	7
13: Sediments, soils, ores, ar	558	354	137	17	418	140
14: Other materials	34	34	34	2	34	0
15: Surfaces, films and enginered nano materials	4	1	1	4	0	4
Totals	**5360**	**3049**	**830 ***			

Table 1: Numbers of CMCs, analyte-matrix combinations, analytes and NMIs providing services for each of the CMC Categories as of 14/12/12, and comparison with CMC numbers from December 2008. *The same analytes appear in a number of categories and the total number of analytes is approximately half the number of analytes calculated by summation of analytes per category.

During the same period the RMOs have been active in coordinating regional comparisons. The activity in each RMO is listed below:

- AFRIMETS has organized 1 Key Comparison in the organic analysis field. Within SADCMET 2 proficiency testing (PT) schemes have been running in inorganics and microbiology, a 3 PT studies have been run in food analysis. Five training workshops in metrology have also been organized
- APMP has organized 10 APMP Key Comparisons (7 completed), 7 Supplementary Comparisons (3 completed) and 24 APMP Pilot Studies (20 completed). The majority of the comparisons have been either in the gas or food areas;
- COOMET has organized 5 COOMET Key Comparisons (3 completed), 2 Supplementary Comparisons and 18 COOMET comparisons (8 completed). The majority of the comparisons have been in the gas and electrochemistry areas.
- EURAMET (previously EUROMET) has organized 8 EURAMET Key Comparisons (5 completed), 5 Supplementary Comparisons (4 completed), 31 EURAMET Comparisons (23 completed) and 9 EURAMET Research Projects (8 completed). The majority of the comparisons have been in the gas area;
- SIM has organized 1 SIM Key Comparison and 2 Supplementary Comparisons, in the organic and gas and inorganic analysis fields respectively.

3.2 Changes in needs and issues arising in the period 1999-2012

3.2.1 Improving the efficiency and effectiveness of the support of CMCs by Key Comparisons

At the very start of the CIPM-MRA in 1999, it was evident that with the very large number of measurands to be covered by the CCQM (3049 analyte-matrix combinations by the end of 2012), only a very small number of measurands would be studied directly in key comparisons, and that processes for extrapolating this performance to other measurands would need to be put in place. This led to the development of the 'how far the light shines' concept, with each comparison protocol requiring a statement on the range of CMCs that could be underpinned by the results of the comparison.

In about 2006 it became clear that the very wide scope of the activities of the CCQM, together with the rapid expansion of the number of actively participating institutes, required an alternative strategy for organizing key comparisons to effectively and efficiently cover CMC claims. The IAWG recognised in particular the problem of supporting a wide range of measurement results on natural matrix samples and began developing a more flexible approach to testing CMC claims based on the concept of demonstrating the "core capabilities" required to deliver the CMC. This approach was adopted by an *Ad hoc* Working Group on Efficient and Effective Testing of CMC Claims (EETWG), which was established by the CCQM in April 2007, as the most effective way of achieving its mandate to provide recommendations to the CCQM on how to deal best with the ever increasing problem of the need for more and more key comparisons arising from the current modus operandi by developing policies to minimize the number needed to underpin the CIPM MRA without compromising their effectiveness. The result was the elaboration of a system to test CMC claims based on demonstrations through KCs of the "core capabilities" required to deliver the CMC.
In April 2011 the EETWG completed its work and was closed. The results have been presented in a paper.

Within the IAWG, it was decided to use the **core capability** approach to designing key comparisons for complex matrix samples alongside the traditional type of key comparison which is retained for applications such as calibration solutions. An important aspect of the IAWG approach in making the most efficient use of resources was to develop the core capability approach in a way which avoided designing samples and comparisons specifically to test core capabilities and allowed the use of real matrix samples which also address high priority measurement applications. This approach facilitates the use of existing candidate reference materials for key comparisons, with the selection of suitable materials being based on their suitability to meet the requirements of a rolling five year plan for comparisons. The IAWG has also developed a comprehensive guide to facilitate the use of core capabilities, addressing both organisation of key comparisons and subsequent review of CMCs.

Within the OAWG, the EETWG recommendations led to a strategy to plan a list of "Track A" comparisons over 5 year periods that allow a participating NMI to benchmark and demonstrate a generic capability for the delivery of reference measurement services for organic analysis. Two generic categories comprise the **Track A core comparisons**:

- Primary calibration reference services (pure substances and standard solutions, Fig. 2)
- Accuracy control services (matrix materials)

In addition the WG outlined:

- "Track B" key comparison which would involve the direct comparison and demonstration of equivalence of the outputs of the measurement capabilities, i.e. the CRMs or PT materials which NMIs/DIs were value assigning
- Track C comparison for a specific measurement issue many institutes wished to have a specific comparison for

- "Track D" studies in new and emerging areas and where further investigation of specific techniques may be warranted

The GAWG developed a process of '**core comparisons'** for stable binary mixtures, where regular participation in any gas core comparison (for any analyte-matrix combination covered by the core comparisons) could be used for support of CMCs of all core gas mixtures.

In addition to the different types of Key Comparisons mentioned above, so-called Pilot Study comparisons may be organized as feasibility studies, benchmarking and learning comparisons. For reasons of efficiency, if possible, these Pilot study comparisons are carried out as an annex to a Key Comparison.

3.2.2 Dealing with new emerging fields/needs

In the last 15 years the CCQM WGs have had to react to changing and expanding numbers of stakeholders and sectors with measurement traceability needs. Some examples from the Working Groups are given below:

In the last five (5) years, there have been a number of strong trends driving developments in the GAWG work programme:

- increasing relationships with international bodies, e.g. WMO and IAEA, have led to new priorities in the work programme focussed on lower concentrations of atmospheric gases, especially greenhouse gases (GHGs) for the maintenance of long term stable values at very high levels of precision for the analysis of trends in the atmosphere over long periods of time.
- increasing priorities from national and regional legislation for population protection, air quality and occupational exposure with a demand for smaller uncertainties.

The NMIs have developed new capabilities and measurement standards to respond to these needs, and the CCQM GAWG has organized comparisons to demonstrate global equivalence. In particular the GAWG has advised that the BIPM laboratory programme includes activities to coordinate comparisons for greenhouse and air quality gases, for which the uncertainty of measurement standards is critical, to ensure the long term accurate global monitoring of these species.

In the Organic analysis field over the period of the last 15 years comparisons have expanded to include a wide range of clinical, environmental, food, forensic and drugs in sport applications. Key comparisons have largely fallen into three categories looking at mass fraction assignments of the organic analyte content of pure compounds, standard solutions and matrix materials. One of the very important activities of the group has been to examine different methodologies for the purity assessment of pure organic calibrators and the BIPM has taken the lead on providing support for this series of comparisons. The knowledge gained from this series has been extraordinary. The OAWG members would universally agree that the program on purity assessment has led to significant improvement in the processes in place within NMIs and DIs carrying out these activities. This is essential when the demands of the user community for SI-traceable pure organic calibrators are continually increasing as a result of activities such as, for example, international clinical standardization programmes.

During its 15 year history, the level of measurement capability demonstrated by IAWG participants in the key comparisons and pilot studies has improved beyond all recognition. For example:

- A very wide range of analytes have been addressed in the comparisons to date, including approximately 50-60 elements and 10 anions, isotope ratios and delta scale isotopic values, organo-metallic compounds (speciation) and inorganic compounds or complexes.

- At least ten different measurement techniques, ranging from classical chemistry to the most advanced instrumentation, are in regular use, often with several employed in the same comparison.
- ID-ICP-MS has been established as the reference method of choice for a wide range of measurement applications and the underlying principles of high accuracy neutron activation analysis (NAA) have been developed so that it could be considered as a potential primary method.

Another important aspect for CCQM has been the close relationship between organisation of comparisons and production of certified reference materials, and the expansion in the production of CRMs by NMIs active in the CCQM over the past 15 years. This relationship has developed because of the added information that a comparison can bring in the characterization of a reference material, and secondly the high financial cost of developing suitable materials for CCQM comparisons, which can only be justified within national programmes if the materials are primarily intended to be developed as CRMs.

The running of pilot studies has been a prevalent activity within the CCQM in the period 1999-2012 (115 stand-alone pilot studies were completed in this period) in order to develop and test metrological approaches in new fields or new applications. For two of the original four WGs (GAWG and EAWG), the number of pilot studies was considerably smaller than the number of key comparison, indicating that a sizeable portion of the methods and capabilities in NMIs were at a mature level, but that developments into new analytes and technologies were taking place. In the remaining two original WGs (OAWG and IAWG) the number of stand-alone pilot studies and key comparisons was about equal, indicating that a greater proportion of NMI capabilities were in development, and new methodologies were being developed and validated in this period. For the BAWG and the SAWG, which were created at a later date to cover new fields, the number of pilot studies organized has been far greater than the number of key comparisons, indicating a strong emphasis on developing metrology for the field to meet user requirements for accurate and traceable measurement results. For the BAWG, these requirements were described in detail in the BIPM document: "Study of Measurement Service and Comparison Needs for an International Measurement Infrastructure for the Biosciences and Biotechnology: Input for the BIPM Work Programme" Rapport BIPM-2011/02. The BAWG pilot studies have resulted in the following key outcomes:

- substantial developments in NMI inter-laboratory precision for NMIs active in nucleic acid quantitation ;
- elucidated uncertainty budgets (including published guidance) for nucleic acid quantitation by qPCR
- a strategy for SI traceability (via digestion and amino acid (AA) analysis) for peptide measurement results demonstrated in recent Pilot studies.
- Support for the first CMCs for GMOs, nucleic acid and peptide quantitation

The need to develop a metrological infrastructure for novel methodologies in microbial measurements led to the establishment of the CCQM *ad hoc* Steering Group on Microbial Measurements. The field of microbiology is in the middle of a paradigm shift due to innovations in molecular biology and the science of genomics. Traditional microbiologists are tasked with a series of parallel procedures requiring days to weeks to culture an organism that provides quantitative information on a Log scale and often lack the resolution (often genus and species level at best) to lead to a comprehensive understanding of the characteristics that make up microbial identity. Molecular technologies and methods including polymerase chain reaction (PCR) and ultra-high-throughput sequencing (UHTS) of the whole genome provide faster and more reliable detection of organisms for clinical diagnostics, and food and water contamination detection. UHTS allows the entire genome of the organism to be sequenced in hours and provides identity information with strain and sometimes the individual clone (e.g., the identity unique to an individual host) level resolution. Qualitative traditional microbiological methods underpin much of the regulatory framework, however, the limit of detection with quantitative PCR is well below the limit of quantitation of microbes with orthogonal methods and efforts to examine the challenges to quantitation and developing measurement uncertainty are needed. Developing a metrological infrastructure for molecular technologies and methods for microbial, alongside other biomeasurements remains a challenge for the future, with initial activity concentrated on meeting stakeholder needs with respect to accurate microbial identity and quantification.

The requirements for activities in the SAWG led to the extension of its scope to chemical characterization of surfaces relevant for life science applications (in 2007) and objects of nanotechnology (in 2009). The need to further develop metrology in certain areas of surface analysis has been highlighted by the results of pilot studies, an example being electron probe microanalysis (EPMA) pilot studies (CCQM-P80, 81, 95), which have shown that the metrology in EPMA analysis needs further development to achieve traceability. It can be summarized here that the specific activities in the SAWG are mostly requested by high-tech based industry in key sectors of economic growth. Metrologically underpinned methods of surface and micro analysis have direct impact on the quality management systems implemented in industry.

In the field of electrochemical analysis a first round of comparisons on all major pH buffer systems have been completed. A broad range of electrolytic conductivity measurement capabilities have been covered, and research is now centering on the extremes of the range relevant to pure water and, for example, pharmaceutical applications at the low level as well as sea salinity and climate change monitoring at the higher level.

The initiation of metrology research programmes within the RMOs, notably the European Metrology Research Programme (EMRP) within EURAMET, has and is leading to the development of new measurement capabilities for chemical and biological measurements. The requirement to demonstrate the international equivalence of such capabilities has and is shaping the programme of key comparisons developed within the CCQM.

3.2.3 Advising on the BIPM work programme in Metrology in Chemistry

The CCQM has been highly active in advising the CIPM on BIPM Scientific Programme Activities in Metrology in Chemistry, and requires annual reports from the BIPM on progress with its Metrology in Chemistry Programme. The initial CCQM process (2000-2004) for the review of BIPM Programmes (see working documents CCQM/01-24; CCQM/03-18; and CCQM/04-04) was based on review in the expert working groups and analysis of NMI requirements through responses to questionnaires and review and approval by the CCQM. With the increase in activities in the CCQM and the BIPM in Metrology in Chemistry an *ad hoc* CCQM Advisory group was created in 2006, to provide an advisory opinion (CCQM/06-13), approved by the CCQM, on the BIPM work programme (CCQM/06-08) developed from input from NMIs in their responses to programme questionnaires (CCQM/06-03 and CCQM/06-41) for the period 2009-2012. The BIPM programme 2013-2016 (CCQM/10-12) was reviewed by the *ad hoc* CCQM advisory group in 2010, and its opinion (CCQM/10-23) was presented, reviewed and approved by the CCQM. As a result the BIPM work programme was modified (CCQM/10-46) and subsequently a revised programme (CCQM/12-07) was adopted following the decision of the CGPM and the CIPM and the shortening of the work programme to the period 2013-2015.

In 2012 the CCQM Strategic Planning Working Group was created, taking on the role of the *ad hoc* CCQM advisory group, and is working to provide advice on the BIPM work programme so that it meets strategic needs defined within the CCQM Strategy.

4. Stakeholders (who they are and their level of involvement)

The CCQM has been highly active in the organization of workshops with stakeholder and sectorial groups in order to understand their requirement for accurate and traceable measurement results. Since 2004, 8 CCQM Stakeholder Workshops have been organized:

- CCQM Workshop on the Role for Reliable Traceable Microbiological Measurements to Ensure Food Quality and Safety (6-7 April 2011)
- CCQM Workshop on Forensics (12 April 2010)
- CCQM Workshop on the Frontiers of Traceability in Chem/Bio Measurement (22 April 2009)
- CCQM Pharma & Bio-pharma Workshop (4-5 December 2008)
- CCQM Workshop on Gas metrology to support measurements of the atmosphere and of ambient air quality (26 October 2007)
- International Symposium on Certified Reference Materials for Quality of Life (1 November 2006)
- CCQM Workshop on higher-order measurement methods for physiologically significant molecules (13 April 2005)
- Reference Measurement Systems for Food Analysis – CCQM Focus Group Meeting (13 September 2004)

In addition, experts and working groups active in the CCQM have contributed to sectorial workshops that cut across the interests of several CCs such as the BIPM Workshop on Metrology at the Nano scale (18-19 February 2010).

For CCQM activities, the NMIs have the primary link to stakeholders as these are at the national level, and are responsible for influencing the development on national metrology programmes. Examples of these stakeholders are:

- National government departments or agencies such as EPAs, US DEA, US FDA, Japan Police Department
- Transnational policy bodies such as the European Commission
- National and international standardisation and accreditation bodies such as ISO and ILAC
- National and international trade or inspection organizations such as APEC
- Industries across sectors such as food, environmental, clinical, forensic and pharmaceutical, semiconductor and nanotechnology
- National and international professional organisations such as IUPAC and IFCC
- Field laboratories which are the ultimate end-users of the services such as microbiological testing laboratories and harmonization organizations that support them e.g. AOAC International

International stakeholders are invited to specialist workshops and when further collaboration is required, invited 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)

5. Future Scan (2013-2023)

5.1 More efficient and effective underpinning of CMCs

CCQM WGs have started to implement a 'core capability' approach to the organization of Key comparisons, which are expected to lead to the gradual implementation of the rolling programmes with more efficient and effective support of calibration and measurement capabilities (CMCs). The expected benefit of adopting a "core capability" approach is to maintain the number of required key comparisons at manageable levels.

Traditional key comparisons with well developed ‘how far the light shines’ statements will be maintained for areas where the reported uncertainties are critical to the capability (for example, the certification of calibrants and calibrations solutions), or where very specific measurands need to be studied to underpin stakeholder needs in a particular application/sector.

5.2 Support for NMIs to meet new measurement requirements in sectors

5.2.1 New measurement requirements by sector

A number of key sectors will require the development of traceable measurement results and the demonstration of their international equivalence, and amongst these several NMIs have indicated that the healthcare, food and environment sectors will be of particular focus for future activities. Specific examples of important issues and trends in various sectors that are likely to drive the development of NMI services are given below. Future CCQM comparisons would then be selected to establish the international equivalence of these measurement standards and services:

a) Health care

- Requirements to develop Reference Measurement Systems for Diagnostics driven by regulatory requirements, e.g. the EU IVD Directive
- Requirements for underpinning work to assure the traceability of quantitative measurements of nucleic acids, proteins, polysaccharides and cells to the SI, including high accuracy purity assessments.
- Systems biology support (e.g. combined ‘omic’ approaches lipid/cell/gene/protein…) – including interactions in immune systems
- Medical gases
- Predictive medicine requirements for trace level circulating biomarker measurement
- Metrology support for development of point of care *in vitro* diagnostic devices
- Measurement to support bio/pharmaceutical quality, safety and efficacy

b) Food safety and nutrition

- Residue and contaminant quantification
- Microbial identification and quantification
- Food constituent labeling
- Food provenance

c) Environment

- Long-term global, direct and remote monitoring of carbon dioxide and other greenhouse gases
- Development of emission controls on toxic and reactive gases from industrial activities to atmosphere and workplace
- Particulates and nanoparticles in indoor and urban air
- Semi-volatile organic compounds in indoor air
- Emerging contaminants with respect to environmental monitoring
- Isotope ratio measurements for sensitive environmental studies
- Water quality, e.g. requirements from the EU Water Framework Directive
- Management of waste streams (reduction, treatment, and recycling of solid, liquid, gaseous or radioactive waste substances)
- Real time analysis of complex particulate composition (for instance metals and PAH content)

d) Energy

- Emerging hydrogen economy (e.g. measurements of impurities in hydrogen)
- Diversification in the supply of energy gases (e.g. biogas, coal mine methane, shale gas)
- Dissolved gas in water (e.g. methane and methane hydrates)
- Usable energy from bio waste, which may require biological as well as calorific value measurements.
- Industrial biotechnology (harnessing sustainable microbial energy)
- Chemico-physical properties of biofuels
- State of health and of charge of energy storage systems (e.g. batteries in the automotive sector)
- Injection of non-conventional gases into existing gas grids
- Alternative technologies in the photovoltaic systems

e) Manufacturing

- Ultra low levels of water vapour and water vapour permeation
- Zero gas for air monitoring and cleanrooms
- On-line chemical sensors providing intelligent feedback for process control

f) Advanced materials

- Development of metrologically underpinned characterization tools and protocols for analysis of nano-structured surfaces, nano-particles nano-electronics, nano-magnetic and nano-electro-mechanical systems and nano-materials.
- Research towards traceability of toxicity measurements with a focus on chemical and biological characterization of nano-particles.
- Development of new materials with functional surfaces including, biomaterials, meta materials, and hybrid materials
- Electrochemical sensors to monitor and feedback on the performance of smart materials
- Embedded chemical sensors in intelligent buildings

5.2.2 Development of a metrological traceability framework for the measurement of new and more complex analytes

The range and complexity of analytes covered by the CCQM is expected to expand, and this will require technological developments including:

a) Metrological traceability for measurements of new and more complex analytes

The development of SI traceable reference systems, including primary calibrators where applicable, was highlighted by many institutes as a priority for organic and inorganic analysis and bio-analysis.

The challenge of providing SI traceability in conformance with the requirements of the CIPM MRA will need to be addressed, since CMC claims have been published for matrix CRMs using calibrants from the same NMI or another NMI for which there are no CMCs for the pure or solution material, which is the basis of their SI traceability. This has led to exceptions to the JCRB Traceability Rules being proposed for certain inorganic analyte based CMCs.

Many groups within NMIs/DIs are also working on larger molecules of biological significance, and this will lead to more closely coordinated activities between the OAWG and the BAWG, as already witnessed by the joint workshop on purity held in April 2012, including method development and comparisons on larger molecule purity coordinated by the BIPM.

Primary calibrator materials, including isotopic reference materials, be they of organic, inorganic or biological nature, are crucial for the traceability of routine measurement results. Therefore, they are a priority area; however only a limited number of NMIs have currently programmes in this area.

b) Development of an international metrological infrastructure for 'biological' measurements

A lack of higher order reference methods and materials is a major hindrance for deriving traceability and comparability in biomeasurement, and this impacts upon accreditation and regulatory compliance. This is a significant driver for the activities of the *ad hoc* MBSG and the BAWG.

The field of microbiology is in the midst of a step change in measurement capability from traditional tools to molecular technologies. Providing the underpinning metrological science is critical to the successful implementation and integration of molecular technologies to support public health and safety decision making. Activities envisioned by the MBSG in the next 10 years can be classified by the two major thrust areas, namely identity and quantity. However, the breadth and range of analytes considered by the CCQM may be expanded beyond food safety microbiology to include clinical and environmental analytes. This may involve multiple Key Comparisons for viral (RNA, DNA), bacteria, microbial toxins, and eukaryotes including parasites. Key comparisons for measurement methods applied to complex microbial systems including microbiome and biofilms may be considered.

In the field covered by the BAWG, new technological challenges will include:

- rapid increases in availability and use of sequencing, which will require new reference and quality control materials;
- enhanced requirements for protein and cell / interactional and structural analysis;
- requirements for comprehensive imaging, enhanced cell separation and label free counting technologies for cell measurements;
- the establishment of absolute quantification methods for nucleic acids;
- development of control and reference materials for new generation sequencing (NGS);
- development of analytical approaches for the characterization of more complex proteins and DNA modifications, the properties of which are not easily expressed in SI units, but which still involve metrological principles;
- support for the validation of highly multiplexed measurements, including the provision of traceability for ‘horizontal’ (performance) standards;
- increasingly multivariate nature of diagnostics – key comparisons to support ‘panel’ biomarker measurements, also comparisons which bring together different biomolecular measurements (e.g. DNA/protein protein/cell markers);
- cell counting and quantitation, including identification and counting of cells in particular states (viability, proliferation, apoptosis), the proportion of such activities is likely to increase;
- characterization and quantitation of complex eukaryotic cellular systems (including animal and microbial ones).

5.2.3 Logistical requirements/constraints

The availability of candidate CRMs as comparison samples is and will be a key limitation to the future planning of key comparisons. The long term strategic planning of comparisons together with a regular review of available candidate reference materials will enable the CCQM to minimise this constraint.

The process and template used for making ‘Calibration and Measurement Capability Claims’ may require modification so that it is more relevant to the large number of analytes and matrices covered by the CCQM.

6. Rationale for various activities (2013-2023)

6.1 An effective and efficient programme of comparisons to support current capabilities

The CCQM programme of comparisons is being designed to:

- meet NMI/DI needs in the most efficient and effective manner through the use of a ‘core capabilities’ approach
- continue to use conventional key comparisons (with ‘how far does the light shine?’ statements) where the reliability of the claimed uncertainties is critical, or where very specific measurands need to be studied to underpin stakeholder needs in a particular application/sector.

Repeat frequencies of comparisons shall be determined based upon a consideration of:

- The scope of the comparison, i.e. comparisons covering a wider range of capabilities will have many participants and will be repeated more frequently (than comparisons with narrow scope and few participants)
- Number of existing and new CMCs in a category addressed by the comparison
- Performance of participants: if good then the repeat frequency may be longer
- Technological change requiring new comparisons
- Need to cover staff turnover and other organisational changes
- Need to cover new entrants

The consideration of the above points has led to the following recommendations for the organization and periodicity of key comparisons in the various CCQM working groups:

- NMIs making use of the GAWG core comparisons, must take part in one core comparison (such as CO, CO_2, SO_2, NO etc.) every two years (GAWG).
- Ozone key comparison (BIPM-QM.K1): each NMI should participate at least once every eight years, and generally not more often than once every four years (GAWG-based on performance in key comparisons).
- Continuation of key comparisons with ‘how far the light shines’ statements for greenhouse gas and air quality measurement standards where the uncertainty of the demonstrated measurement capability is critical to the application of the measurement standards. These comparisons are included in the activities of the GAWG, which has advised that they should be coordinated within the BIPM laboratory programme, to ensure a uniform worldwide metrological system for the long term accurate global monitoring of these species.
- Natural gas comparisons will be repeated once every six years (GAWG)
- In the field of organic analysis a set of 10 ‘Track A’ Key Comparisons shall be selected to test core competencies covering most of the CMCs in the organic analysis area. The set of 10 studies will be conducted over the next 5 years, with two studies to be initiated per year, one in primary calibration reference services and one in accuracy control services (OAWG)
- The OAWG programme of organic purity comparisons, coordinated by the BIPM, is expected to play a key role in the CCQM activities It consists of a programme of comparisons which strategically covers the purity and calibration solution measurement space, with a set of 4 comparisons covering all small organic molecule based CMCs, as indicated in the diagram below (OAWG), and the extension of the model to comparisons for large organic molecules.

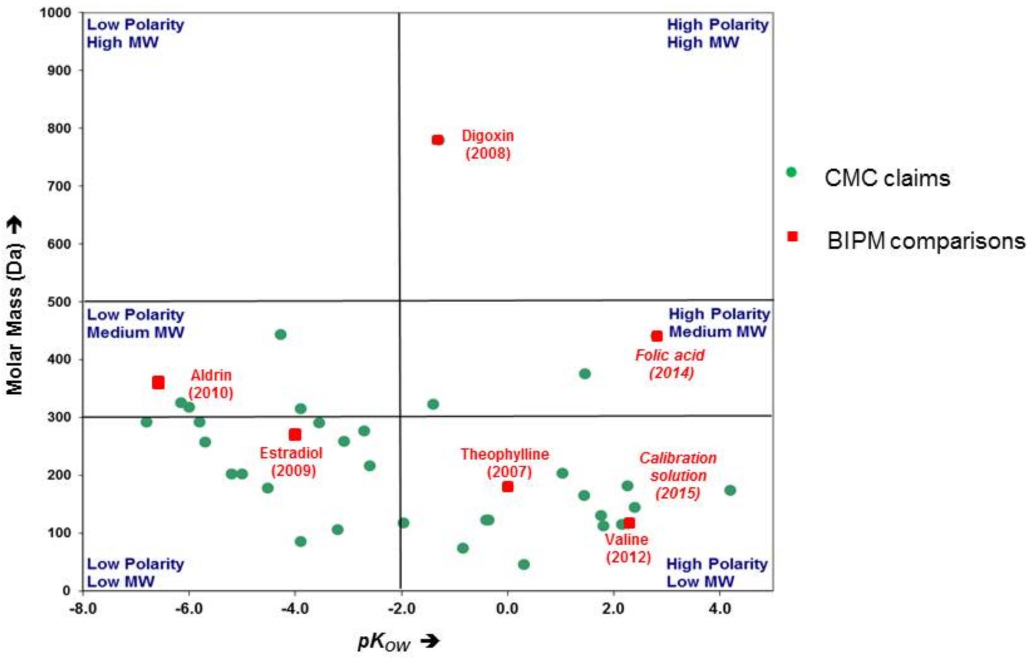

Figure 2. NMI primary calibrator CMC claims for organic compounds as a function of their molar mass (MW) and polarity. The majority of claims fall into 4 categories: 1) Low Polarity, Low MW; 2) Low Polarity, Medium MW; 3) High Polarity, Low MW; 4) High Polarity, Medium MW. A set of 4 'Track A' core key comparisons coordinated by the BIPM under pins all CMCs in these categories.

- The IAWG has proposed the following policy on frequency of participation:
  - Each NMI/DI with current CMCs should participate at least once every two years in a key comparison relevant to its field of application.
  - Each NMI/DI with current CMCs should participate at least once every four years in a comparison which provides a '1:1' KC:CMC check.
  - Every five years the IAWG will declare an appropriate comparison to be a 'benchmarking exercise' for all active participants in order to obtain a direct assessment of performance across the entire IAWG.

- In order to allow flexibility regarding frequency of participation in specific comparisons, the IAWG has also proposed that each NMI/DI should maintain a 'record of participation' in an agreed tabular format in order to demonstrate its overall KC performance during the preceding 7 years.

- Closer links will be established between the comparison schedule and the CRM production plans of NMIs and DIs. This principle will greatly reduce costs by facilitating use of the same materials for both purposes. In order to facilitate this approach, the IAWG has established a rolling forward programme of 'slots' for comparisons and pilot studies based primarily on matrix type and maintains a database of future CRM production plans of its participants.

The links and differentiation with RMO comparison programmes is expected to continue. For example within EURAMET, future comparison will be designed:

- to support CMCs of NMIs/DIs developing new capabilities in the chemical fields
- to provide supplementary comparisons for compliance to European legislation (e.g. Air Quality Directive, WFD, European carbon reduction targets…)

6.2 Support for new capabilities

CCQM pilot studies will be coordinated for activities such as the development of metrology in new application areas, investigation of emerging techniques, and to facilitate collaboration with other expert laboratories outside the CIPM-MRA. The largest number of pilot studies relative to key comparisons is foreseen in areas where the further development of a metrological infrastructure is required, notably for the *ad hoc* MBSG, the BAWG and the SAWG. For the BAWG and the ad hoc MBSG pilot studies will be coordinated for the development of an international metrological infrastructure for biological measurements (as described in 5.2.2.b).

In the area of surface chemical analysis at the nano and micro scale, studies to develop the traceability and comparability of quantitative data will be required for:

- methods of surface chemical analysis at the micro scale (e.g. EPMA, EDS, WDS, AES)
- measurements of amount of matter in a shell for a core-shell engineered nanoparticle (e.g. by XPS, AES, TEM)
- measurements of the amount of matter in a buried organic layer (e.g. by SIMS, XPS, XRR, NR, ellipsometry)
- measurements of composition and spatial distribution of matter for functionalized nanomaterials (e.g. by DLS, XPS, SPM, TEM).
- measurements of composition and spatial distribution of matter for thin film systems (e.g. by XPS, EPMA, XRD, XRR, CRM, AEM)
- determining the accuracy and comparability of nanoscale 3D chemical imaging methods (e.g. SIMS, tomographic methods using X-rays or atom probe techniques)
- quantification of both inorganic and organic contaminants on silicon surfaces
- measurement of concentrations of active proteins at surfaces (e.g. by SIMS, fluorescence microscopy, non-linear optical microscopy).

Methods of surface chemical analysis at the nano and micro scale are integral to the future development of many advanced technologies in the developed world. Therefore, the development of metrologically underpinned surface and micro analysis is strongly requested by industry in key sectors of economic growth with the innovation of new products (cf. e.g. Case study 9, Appendix II) and the solution to production problems.

Studies required in the gas metrology field will follow the research and development activities carried out by various NMI's, including the development of new gas measurement standards, the development of dynamic dilution, spectroscopic techniques, and measurement standards for nanoparticles, aerosols and dissolved gases.

Key areas of inorganic metrology that will require further development will include:

- Providing key comparisons to underpin metrological services at ultra low analyte levels, which present major technical challenges, not least storage and transport of reference materials and comparison samples;
- Determination of more complex and/or labile inorganic or organo-metallic species including nanoparticles, which will require further extensive development of hyphenated methods,

coupling separation science with spectroscopic or other measurement techniques also by NMIs;
- Methods which allow solid sampling and/or quantitative elemental imaging leading to emerging metrological applications of techniques such as GD-MS and laser ablation ICP-MS;
- Matrix specific isotope ratio measurement standards or reference materials, particularly for application areas such as geology, forensics, food adulteration or origin and environmental studies. This will require programmes in the area of Delta values (C, H, O, N) and for absolute metal or other non-metal isotope ratios determined by techniques such as TIMS or ICP-MS.

In the organic analysis field, pilot studies will continue to be used as forerunners for many Key Comparisons in new and emerging areas where further investigation of specific techniques/methods is warranted. For instance, quantitative NMR is a technique which is still being assessed as a high-accuracy reference measurement procedure and measurands which represent a very specific measurement challenge may warrant pilot studies.

In the field of electrochemical analysis future studies will be required for the investigation of measurement standards and reference methods for mixed solvent/low conductivity and pH measurement standards; and measurement standards relevant for sea water salinity and pH.

6.3 Organizational aspects

The CCQM Working Groups have been organized on the basis of assembling in the most efficient and effective way the best globally available expertise, knowledge and competence in the different fields of metrology. The Working Groups all operate under the umbrella of the CCQM and report jointly and when required have periodic inter-disciplinary sessions. In this way the CCQM has also been able to organize almost yearly one or more workshops or symposia with major stakeholders, to bring in expertise not yet available within the NMI/DI community, to address in an open and transparent way the metrological needs of the stakeholders, and to set the necessary priorities.

Further inter-disciplinary cooperation is needed in the near future, for example with regard to moisture-, aerosol- and nano-measurements.

7. Required Key comparisons and pilot studies 2013-2023 with indicative repeat frequency

The number of key comparisons and stand-alone pilot studies per year foreseen for the period 2013-2023 for each of the CCQM working groups is given in Table 2, and is compared to the data available for the period 1999-2012. The approximate number of CMCs currently underpinned by the activities of each of the WGs is also given in the table.

CCQM Working group	**Number* of Key comparisons 1999-2012**	**Number* of (standalone) Pilot Studies 1999-2012**	**Approximate Number of CMCs underpinned by WG activities at the end of 2012**	**Estimated Number of Key comparisons for 2013-2023**	**Estimated Number of (standalone) Pilot Studies for 2013-2023**
Gas Analysis Working Group (GAWG)	**26[‡]**	**9**	**2039**	**30**	**10**
Organic Analysis Working Group (OAWG)	**29**	**34**	**1480**	**30**	**5 to 10**
Inorganic Analysis Working Group (IAWG)	**36**	**38**	**1400**	**30**	**8**
Electrochemical analysis (EAWG)	**18**	**9**	**117**	**15**	**15**
Bioanalysis Working Group (BAWG)	**2**	**20**	**9**	**10**	**10**
Surface Analysis Working Group (SAWG)	**2**	**5**	**4**	**4**	**7 to 10**
***Ad hoc* Steering Group on Microbial Measurements (MBSG)**	**0**	**0**	**0**	**3**	**10**
Total number of CCQM comparisons (1999-2012)	**113**	**115**	**-**	**-**	**-**
Average number of CCQM comparisons per year (1999-2012)	**9**	**9 to 10**	**-**	**-**	**-**
Estimated total number of CCQM comparisons (2013-2023)	**-**	**-**	**-**	**122**	**65 to 73**
Estimated average number of CCQM comparisons per year (2013-2023)	**-**	**-**	**-**	**12**	**7**

Table 2: Estimations of the number of key comparisons and stand-alone pilot studies that are foreseen to be run each year during the period 2013-2023 by each of the current CCQM WGs, and data from 1999-2012.

***The numbers of comparisons/studies organized by each working group have been corrected to take into account comparisons/studies organized jointly by two working groups.**

[‡] GAWG key comparison totals does not include the first series of gas metrology key comparisons started in 1998.

The total number of key comparisons and stand-alone pilot studies that will be coordinated (122 KCs and 65 to 73 pilot studies, a total of 187 to 195) in the ten year period 2013-2023 is comparable to the numbers in the thirteen year period 1999-2012 (113 KCs and 115 pilot studies, a total of 228).

The figures above indicate that the total average number of key comparisons run every year will increase from an average of 9 (in the 1999-2012 period) to an average of 12 a year in the next ten year period (2013-2023). Conversely, the total average number of pilot studies run every year will decrease from an average of 9 to 10 (in the 1999-2012 period) to an average of 7 a year in the next ten year period (2013-2023). Overall, this will mean that the total number of key comparisons and stand-alone pilot studies will remain constant at 18 to 19 per year (in 1999-2012) to an estimated average of 19 per year (for 2013-2013).

A number of the established WGs (OAWG and IAWG) foresee a considerable reduction in the number of needed pilot studies, whilst additional pilot studies are foreseen in the newly established working group, the *ad hoc* MBSG.

The continuation in the estimated combined total number of comparisons and pilot studies foreseen for 2013-2023, can be explained by a number of factors:

- A stabilization in the number of key comparisons required to underpin CMCs in the organic, inorganic and gas areas through the adoption of a core capability comparison scheme;
- An increase in the scope of activities of the CCQM (with the establishment of the ad-hoc MBSG) leading to new comparisons in this field, and increasing the total number of comparisons and studies covering biological capabilities;
- An increase in the overall estimated number of comparisons and pilot studies required in the surface analysis area;
- An increase in the estimated number of pilot studies required in the electrochemical analysis area.

8. Resource implications for laboratories for piloting comparisons

For CCQM comparisons, NMIs piloting key comparisons must allocate resources for two distinct activities, notably:

a) Preparation and characterization of the measurement standard or sample material to be used in the comparison, including the value assignment of the measurement standard or sample material;
b) Organizing, conducting and reporting the comparison.

Samples prepared for key comparisons must be of sufficiently high quality to meet the requirements of the comparison, which in reality means that the preparation and characterization of these samples must follow the processes used for certified references materials (CRMs). Related costs can be far greater than those required to coordinate the comparison, and for this reason a large number of CCQM comparisons are being run on candidate reference material samples, where the cost of material preparation is borne by the CRM production activity, and not considered as part of the comparison costs. Nevertheless, the resources to prepare appropriate materials for comparisons is partially included in Table 3, as this can be a limitation in having materials available. However, once a material is available there is added value for the NMI proposing its candidate CRM as a comparison sample as further information and measurement results on the material will be obtained.

The resources required to coordinate a comparison vary depending on the type and difficulty of the measurement and the stability of the measurement standard/ material. A break down on the range of costs/resources required to pilot a comparison for the various CCQM WGs is given in Table 3 below.

CCQM Working group	Minimum resources for **Sample Preparation** in Person Months (PM)	Maximum resources for **Sample Preparation** in Person Months (PM)	Minimum resources for **Comparison Coordination** in Person Months (PM)	Maximum resources for **Comparison Coordination** in Person Months (PM)	Minimum resources for **Comparison PARTICIPATION** in Person Months (PM)	Maximum resources for **Comparison PARTICIPATION** in Person Months (PM)
Gas Analysis Working Group (GAWG)	**2**	**12**	**3**	**6**		
Organic Analysis Working Group (OAWG)	**0.5***	**20**	**6**	**12**	**1**	**12**
Inorganic Analysis Working Group (IAWG)	**12**	**18**	**6**		**1**	
Electrochemical analysis (EAWG)	**1**	**3**	**2**	**6**	**1**	**2**
Bioanalysis Working Group (BAWG)	**12 (includes comparison coordination)**	**36 (includes comparison coordination)**			**1**	**12**
Surface Analysis Working Group (SAWG)	**6**	**18**	**6**	**12**	**1**	**6**
***Ad hoc* Steering Group on Microbial Measurements (MBSG)**	**6**	**24**	**3**	**12**		

Table 3: Resource estimates in Person Months (PM) required for: a pilot laboratory to a) prepare and characterize samples for comparisons and b) to coordinate the comparison; and resources required for a laboratory to participate in a comparison.

*This would only be the case where a material already exists as a CRM and needs only to be packed for shipping

9. Summary table of comparisons, dates, required resources and the laboratories already having institutional agreement to pilot particular comparisons

Information by Working Group is contained in the attachment.

10. Document Revision Schedule

1 year for exceptions
2 year updating of all lists
4 year major revision with extension of period covered by rolling programme

Appendix 1 :BIPM Laboratory activities as part of the CCQM Strategic Plan

CCQM Strategy document references to laboratory activity at the BIPM

The BIPM Chemistry Department coordinates key comparisons and pilot studies prioritized by the CCQM in response to NMI needs (5 key comparisons and 7 stand-alone pilot studies (2000-2012), with over 250 NMI participations in these comparisons). The BIPM activities have been strategically focused to meet CCQM comparison needs for:

> a) greenhouse and air quality gases, for which the uncertainty of standards is critical, to ensure the long term accurate global monitoring of these species, including BIPM.QM-K1 for surface ozone;
> b) the purity assessment of pure organic calibrators (source of traceability for all measurements of the amount of organic species). Coordination of an on-going series of 4 comparisons covering all small organic molecule based CMCs, with an extended model of comparisons for large organic molecules.

The BIPM Chemistry Department provides the Secretariat for the Joint Committee for Traceability in Laboratory Medicine (JCTLM)

BIPM Laboratory Activities to meet future CCQM Strategic Plans

The future CCQM strategic plan relies on a range of comparisons underpinning a broad range of NMI capabilities through core capability comparisons in addition to specifc analyte-matrix comparisons which are required when uncertainties are challenging and critical to the application of the capability.

In consequence, CCQM comparisons vary amongst:

a) irregular/'one off ' comparisons to comparisons with regular repeat periodicities to closely monitor long term performance of capabilities;

b) comparisons which underpin fundamental and more stable capabilities (e.g. primary reference materials/calibrators) versus comparisons that underpin applied and changing capabilities (e.g. complex matrix reference materials)

BIPM laboratory activities enable a long-term commitment to comparison coordination, which is best adapted to periodic comparisons, underpinning fundamental capabilities, and allowing close monitoring of their performance. The CCQM strategy document foresees BIPM coordinated CCQM comparisons for
a) primary calibrators for prioritized green-house gases and air quality gases, and
b) purity assessment capabilities for primary reference materials for small and large organic molecules

The on-going requirement for these comparisons can be best met through BIPM laboratory coordination of the comparisons, since:
a) the comparisons are fundamental to a broad range of NMI services and require a long term commitment to their coordination that can be met by the BIPM;

b) comparability at the smallest levels of uncertainty need to be demonstrated for high impact measurands on a continued basis; this is bet met with a long term comparison programme, as established and demonstrated at the BIPM.

The CCQM tables of future comparisons do not yet fully cover the period for 2013-2023, however the BIPM has already been identified as the comparison coordinator for the comparisons in the tables below. The longer term repeat frequencies of these are described in the CCQM Strategy Document, and 10 to 15 CCQM key comparisons are to be coordinated by the BIPM out of a total of 126 foreseen for the period 2013-2023.

Required Key comparisons and pilot studies 2013-2023 with indicative repeat frequency from CCQM OAWG Strategy Document

Year	Primary Reference Track A	Accuracy Control Track A
2011	Non-polar pure organic (300-500 mol weight) [BIPM]	Polar organic in food [GLHK/NIM]
2012	Polar pure organic [BIPM] (100-300 mol weight)	Non-polar organic in abiotic matrix [IRMM]
2013	Polar pure organic [BIPM] (300-500 mol weight)	Polar organic in biological matrix [NIST]
2014	Non-polar multi-component calibration organic solution	Large molecular weight organic in biological matrix
2015	Polar multi-component aqueous solution [BIPM]	Non-polar organic in water
2016	Volatiles in organic solution	Non-polar organic in food
2017	Non-polar pure organic (100-300 mol weight) [BIPM]	Polar organic in abiotic matrix†
2018	Large molecular weight pure organic (500-1000 mol weight)	Non-polar organic in biological† matrix
2019	Polar pure organic (300-500 mol weight) [BIPM]	Large molecular weight organic in biological matrix
2020	Non-polar multi-component calibration organic solution [BIPM]	Polar organic in food†
2021	To be defined	Non-polar organic in abiotic matrix†
2022	To be defined	Polar organic in biological matrix†
2023	To be defined	To be defined

Summary of all planned CCQM Key Comparisons where the BIPM is indicated as the coordinating laboratory contained in Annexed lists (as of 23/05/13) of comparisons produced by CCQM WGs (OAWG comparisons listed above were not transcribed to the Annex list)

Sub Area	Reference No.	Description	Pilot (Coordinating) Laboratory	Expected Start date	Estimate of resouces in person months (PM) for piloting and particpating (per particpant)	Rational for Key Comparison	Interested /agreed/expressed by:	How far does the light shine?
GAWG	BIPM.QM-K1	Ozone at ambient level	BIPM / 20	2007 - ongoing			Agreed	BIPM QM K1 Reports
GAWG	CCQM-K82	Methane in air : preparative comparison	BIPM	2013		Atmospheric and air quality	Agreed	
GAWG	CCQM-K90	Formaldehyde in air	BIPM	2014		Atmospheric and air quality	Agreed	
GAWG	CCQM-KXX	KC (ambient CO_2)	BIPM with NIST	2015		Atmospheric and air quality		
GAWG	CCQM-KXX	Core KC (NO)	BIPM	2016		Atmospheric and air quality		
GAWG	CCQM-KXX	KC (NO2)	BIPM	2017		Core mixtures (stable binaries and multi-components)		
GAWG	CCQM-KXX	Core KC (Reactive gas)	BIPM	2018		Core mixtures (stable binaries and multi-components)		
GAWG	CCQM-KXX	KC (HCHO, repeat)	BIPM	2020		Atmospheric and air quality		
OAWG	CCQM-K78	Mass Fraction of Organic Calibration Solution	BIPM	2013				
BAWG	CCQM-Kxxx/Pxxx	Peptide Purity	BIPM/NIMC	2014		Study design in discussion with interested participants. C peptide 31aa.		

Appendix II: Examples of the impact of CCQM Comparisons and the calibration and measurement capabilities they support

A) Impact of CCQM Activities in the Healthcare Area

Case Study 1: International Equivalence, Accuracy and Traceability for Kidney Function Marker and Heart Disease Risk Factor Measurements

Accuracy and acceptability of chemical and biochemical measurement results in the healthcare sector are critical to the global economy and to the well-being of our citizens. In the U.S., for example, over $2.5 trillion[1] is spent annually on healthcare with 10-20%[2] of this cost associated with measurements. 70%[3] of medical decisions are based upon results from tests performed in a medical laboratory; yet only about 10% of the ~700 most-often-performed laboratory tests have an internationally-recognized measurement infrastructure underpinning these measurements[4]. In Germany, it is estimated that the costs of repeat measurements amounts to more than 1.5 billion US$[5] per year. There are therefore strong drivers to improve the traceability, quality and number of measurands covered by an internationally recognized measurement system. Comparisons organized by the CCQM have addressed both improvements and the needed increase in reference material/measurement provision.

Since 1998, 10 CCQM Pilot Studies and 14 CCQM Key Comparisons have been completed in support of healthcare measurements. These CCQM Comparisons in the Healthcare/Clinical Diagnostics sector have resulted in significantly increased capacity in this area, with nine NMIs/DIs providing services in support of healthcare measurements, from a starting point of two at the start of the CCQM comparison programme. There are now multiple sources of internationally recognized measurement services (CRMs, Value-assigned PT Samples, Calibration Services) for clinical diagnostic markers that are recognised both in the BIPM KCDB and the JCTLM Databases. Two examples for cholesterol and creatinine are described below.

(**Note:** The creation of the successful Joint Committee on Traceability in Laboratory Medicine - JCTLM in 2002, together with the IFCC and ILAC, and with the full support of stakeholders from the *in vitro* diagnostics community, was made possible as a result of the establishment of the CCQM in 1993 and the Chemistry Department of the BIPM in 2000, which has provided the secretariat for the successful running of the committee).

Cardiovascular diseases, including heart disease, are the world’s largest killers, claiming 17.3 million lives a year. Risk factors for heart disease include raised cholesterol levels, which has led to national programmes being developed to measure and allow populations to control their cholesterol levels. In 1998 the CCQM conducted a pilot study (**CCQM-P6**) to investigate capabilities for five NMIs to provide metrologically traceable measurement results of cholesterol in human serum. The measurements were repeated in 2000 in a key comparison (**CCQM-K6**) with much improved results. The improved results in the Key Comparison resulted from extensive discussions of the entire

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[1] U.S. Department of Health and Human Services, Centers for Medicare and Medicaid Services, National Health Statistics Group http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/tables.pdf Table 1 as of 27 Dec 2012.
[2] Medical Laboratory Observer; On Laboratory Medicines Front Lines: The Laboratory, The Washington Post, December 25, 1993; The Cutting Edge--Doctors Can Help Reduce Cost of Laboratory Tests, The Washington Post, March 28, 1989
[3] Quest Diagnostics, www.curran-connors.com/localversions/online-ar/quest2005/letter.html
[4] IFCC, www.bipm.org/cc/JCTLM/Allowed/Dec.07_Symposium/JCTLMSymp07-03.pdf
[5] German Health Report of 1998 www.gbe-bund.de

measurement process, leading to discovery that the accuracy limiting step was associated with the sample hydrolysis procedure used to free cholesterol from sample matrix components, and optimisation of these procedures allowed the excellent results to be obtained.

Creatinine is a clinically important diagnostic marker for kidney function. Routine clinical tests are mostly based on enzymatic reactions that are subject to interferences from various substances coexisting with creatinine in blood or serum samples. Use of different methods of analysis, different reagents, etc., may lead to significantly different results. Therefore, high-order reference methods and reference materials are needed to maintain adequate accuracy in routine measurements for creatinine. The **CCQM-K12** study to assess the reference measurement capabilities of NMIs utilized two frozen serum materials, and the participating NMIs demonstrated that they could successfully measure serum creatinine at normal and elevated levels with expanded uncertainties of less than 0.8% (relative). In **CCQM-K80**, the assigned creatinine values of seventeen CRMs, all intended for sale to customers, were compared under repeatability conditions. The results demonstrated that the participating NMIs have the capability as a group to successfully assign creatinine values with a relative bias of ±2 % or less in frozen or lyophilized human serum reference materials as delivered to customers. The demonstrated capabilities are more than sufficient for current needs in the clinical laboratory; decreased uncertainty in measurement results leads to fewer repeat measurements (less cost) and improved diagnostic/treatment decision-making.

Case Study 2: Development of SI traceable reference measurement systems for peptides and proteins including for the monitoring and treatment of diabetes

The accurate measurement of the concentration of small proteins and peptides is of prime importance in the monitoring and treatment of highly prevalent diseases and medical conditions including diabetes. The WHO currently estimates that 347 million people worldwide have diabetes. Advances in modern physico-chemical characterization methods permit the amount of many small proteins and most peptides to be assigned in SI units. This requires the establishment of reference measurement systems with a clear definition of the measurand and this is a core strategy for CCQM as it ensures long term accuracy and comparability of measurement results. The **CCQM-P55** series of studies on protein/peptide quantification have made significant progress in this area, supporting NMIs that wish to provide protein reference measurement services, predominantly to support the clinical diagnostic and biopharmaceutical community.

An initial publication by the **CCQM-P55** co-ordinating laboratories (Arsene et al. *Anal. Chem.* **2008,** *80,* 4154–4160 Protein Quantification by Isotope Dilution Mass Spectrometry of Proteolytic Fragments: Cleavage Rate and Accuracy), followed by the results from the **CCQM- P55.1** study have now enabled participating NMIs to claim generic CMCs for peptide measurement which has underpinned the development of reference methods and materials for human GH in serum, and those relevant to the monitoring and treatment of diabetes, notably insulin, HbA1c and C-peptide.

Case Study 3: Supporting national and international program for steroid hormone measurements to help in the diagnosis, treatment and prevention of breast, testicular and prostate cancers

Laboratory testing of blood levels of the steroid hormones testosterone and estradiol are critical for the diagnosis and treatment of a number of serious conditions and chronic diseases, such as polycystic ovarian syndrome; androgen deficiency in men, breast cancer, testicular cancer; infertility; osteoporosis; and pituitary disorders.

It is estimated that over a 20-year period, testosterone deficiency is projected to be involved in the development of approximately 1.3 million new cases of cardiovascular diseases, 1.1 million new cases of diabetes mellitus, and over 600,000 osteoporosis-related fractures. In year 1, the attributed cost burden of these diseases was approximately $8.4 billion. Over the entire 20-year period, testosterone deficiency may be directly responsible for approximately $190–$525 billion in inflation-adjusted U.S. health care expenditures[6].

Research findings suggest that postmenopausal women with elevated estrogen levels are at increased risk for developing breast cancer[7]. The American Cancer Society estimated for 2013 that about 232,340 new cases of invasive breast cancer will be diagnosed and about 39,620 women will die from breast cancer in the US[8].

Accurate and reliable testing of testosterone and estradiol are essential for formulating evidence-based clinical guidelines that are based on multiple research studies performed in different laboratories and at different times. Further, they are crucial for the implementation of such clinical guidelines to assure appropriate, consistent patient care and disease prevention. Testosterone and estradiol tests currently lack the necessary accuracy and reliability and thus limit appropriate patient care and disease prevention. This is recognized and described by multiple professional organizations such as the Endocrine Society[9,10].

The basis for accurate testing and thus appropriate patient care are primary standards. They ensure that reference measurement procedures and tests used in patient care can be calibrated and traced back to one common standard.

In the US, the CDC began a project to standardize hormone measurements in 2007 in order to ensure accurate and comparable results across testing systems (assays), laboratories and over time. The two key elements of the solution are the development of reference materials that have highly accurate certified values, and reference methods that allow highly accurate measurements.

The CCQM comparison **CCQM-K55.a**, coordinated by the BIPM and the NMIJ, allowed NMIs to compare and improve their capabilities for the value assignment of primary standards of the pure steroid hormone estradiol. Subsequently, an estradiol certified reference material was produced by NMIJ and this has been internationally accepted and published in the JCTLM list of reference materials of higher metrological order. It is now also used, for instance, as a primary calibrator for the CDC program for steroid hormone harmonization. Similarly, other pure steroid hormones have been reviewed and internationally accepted and published in the JCTLM list of reference materials.

The availability of such materials greatly facilitated the implementation of ongoing standardization efforts and helps to sustain such multi-year efforts.

In addition to work programmes on the pure materials there have been two CCQM key comparisons covering steroid hormones in human serum (**CCQM-K63.a** and **b** for cortisol and progesterone) . These underpin the internationally comparability of the steroid hormone matrix CRMs produced for the clinical community. The availability of such matrix based materials for the validation of methodologies is essential and forms a crucial component of successful international and regional standardization programs.

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B) Impact of CCQM Activities in the Environmental and Climate Change Monitoring Area

Case Study 4: International Equivalence, Accuracy and Traceability for Greenhouse Gas and Surface Ozone Monitoring

There is considerable global focus on greenhouse gas (GHG) emission quantification and verification and its impact on climate change and global warming. Possible developments in cap and trade approaches and legislation relative to these emissions will lead to a major increase in demand for GHG measurement systems. The consistency, fairness and accuracy of these will need to be assured. The long term monitoring of greenhouse gases (GHG) places stringent requirements on the permitted uncertainties of primary standards to which these measurement results are traceable. Data Quality Objectives for the monitoring of greenhouse gases have been documented by the WMO-GAW programme and currently stand at: ± 0.1 µmol/mol (Northern Hemisphere) and ± 0.05 µmol/mol (Southern Hemisphere) for carbon dioxide; ± 2 nmol/mol for methane; ± 2 nmol/mol for carbon monoxide. The CCQM has increased its collaborative work started in 2001 with the WMO, which signed the CIPM-MRA in 2010 to permit two expert laboratories to participate in the CCQM comparisons on greenhouse gases and ozone. The CCQM has coordinated key comparisons for ambient level of CO_2, CH_4 (**CCQM-P41** and **CCQM-K52**), N_2O (**CCQM-K68**), and halocarbons. NMIs active in the CCQM provide the World Calibration Centre (WCC) & Central Calibration Laboratory (CCL) function for the WMO Global Atmosphere Watch (GAW) on volatile organic compounds (VOCs) and surface ozone. The degree of equivalence of surface ozone measurement standards has been demonstrated on an on-going basis with the key comparison **BIPM-QM-K1**, coordinated by the BIPM. As a result of the BIPM activity the relative standard deviation of results in ozone measurement standard comparisons is approaching 0.1% relative, a level which needs to be maintained in order to meet the data quality objectives for the long term monitoring of tropospheric and surface ozone. This is a considerable improvement from the 1% relative agreement demonstrated with the regional comparison EUROMET 414 in 2002.

Case Study 5: International Equivalence, Accuracy and Traceability for Sea Salinity Measurements and Climate Change

Thermohaline circulation (THC), a part of the large-scale ocean circulation that is driven by global density gradients created by surface heat and freshwater fluxes, plays a vital role in maintaining the current climate. It is driven by differences in seawater density, which depend on temperature and salinity, and the measurements of salinity, based on conductivity measurements, is an important input quantity for global oceanographic observation and monitoring systems as well as for oceanic and climate modelling.

The CCQM comparison **CCQM-P111** with the participation of oceanographic laboratories has demonstrated the current uncertainty in primary salinity measurement. Uncertainties in measurement results traceable to a conventional Standard Sea Water (SSW) reference material were five times lower than the ones which could be achieved with SI traceable results. The latter uncertainties would be too large for oceanographic purposes. The outcome of the study led to increased awareness in the oceanographic community to metrology issues, as manifested by The International Association for the Properties of Water and Steam‘s (IAPWS) request for support from the metrology community for oceanography and climatology and its establishment of the “Joint Committee on the Properties of Seawater” (JCS) in collaboration with the Scientific Committee for Oceanographic Research (SCOR) and the International Association of the Physical Science of the Oceans (IAPSO). This new committee will closely collaborate with the international metrology community and among its tasks are:

-to globally coordinate research and the development of measurement standards related to the properties of seawater across different scientific communities,
- to identify developing needs for measurement standards and encourage research in those areas, and
- to work towards international and interdisciplinary uniformity and consistency of the measurement standards and measurement procedures used in oceanography

C) Impact of CCQM Activities in the Food Area

Case Study 6: International Equivalence, Accuracy and Traceability for Essential Nutrient Measurements (Selenium)

An essential nutrient is a nutrient required for normal body functioning that cannot be synthesized by the body at all, and must be obtained from foodstuffs. An example is Selenium (Se), which has long been recognised to have both toxic and beneficial effects. Low Se intake is associated with several diseases and the use of selenium-containing or enriched supplements as well as Se-enriched foods is well-established. More recently, human supplementation studies have shown benefit in reducing the risk of cancer incidence (e.g. for liver, prostate, colo-rectal and lung cancers). Moreover, studies with pre-clinical models suggest that cancer cells are sensitised to chemotherapy by Se, enhancing the effectiveness of chemotherapy drugs, whilst normal cells may be protected. The development of well-validated measurement methods for this important application area, together with appropriate chemical measurement standards and matrix reference materials, is actively underway at a number of institutes which participate in the CCQM, together with a series of pilot studies and key comparisons (see below) in order to establish equivalence between their measurement results and materials. This work has facilitated rapid progress in developing new and demanding methodology: the overall level of Se in the test materials has been progressively reduced (from total Se of 315.5 mg kg^{-1} to 17.3 mg kg^{-1} to 0.06 mg kg^{-1}) whilst the complexity of the test sample matrix has increased. The aim has been to address three key analytical applications: selenium pharmaceutical supplements, enriched foods, and clinical measurements.

Pilot studies and key comparisons for selenium and selenium compounds
CCQM-P86: Analysis of total selenium and selenomethionine in pharmaceutical supplements (2006)
CCQM-K60 (and CCQM-P86.1): Total selenium and selenomethionine in selenised wheat flour (2008)
CCQM-K107 (and CCQM-P86.1): Elements and selenium speciation in human serum (ongoing)

Case Study 7: International Equivalence, Accuracy and Traceability for the measurement of GMOs in Food

Food labeling regulations in a number of economies around the world, most notably the EU, require the content of genetically modified organisms (GMOs) to be labeled on food stuffs.
The **CCQM-P44/K60** and **CCQM- P113/K86** study series have supported a number of NMIs in demonstrating their capability in characterising GM food reference materials and providing calibration services. Furthermore the knowledge accrued in determining the associated measurement uncertainty and variability of results obtained with different DNA extraction techniques was published in peer reviewed literature, and has subsequently been sent to the European Union Reference Laboratory for GMOs in Food and Feed (EU-RL GMFF).

CCQM-K86 and its paired **CCQM-P113.1** pilot study showed that it was possible to accurately determine the relative quantity of two genomic DNA targets present in a plant tissue. Whilst EU legislation with respect to GM analysis has typically used the GM content of samples expressed in terms of mass per mass equivalents, derived from genomic calibrants, there has been a move in Europe and other countries to express the GM content in terms of haploid genome equivalents (copy number ratios), that can be facilitated using plasmids or matrix-matched calibrants certified for their copy number ratio. The participating NMIs have confirmed that the expression of the GM content of a sample in terms of copy number ratios could be metrologically traceable in an operationally-defined manner by using, e.g., a common plasmid CRM for calibration that is certified for the relative quantity of the two genomic targets. Moreover, results obtained by quantitative PCR were in agreement with the digital PCR results (obtained without the use of an external calibrant). The GM/non-GM ratio levels tested in **CCQM-K86** were relatively low and below the GM labelling thresholds currently in place worldwide. The levels tested in this key comparison were therefore particularly relevant for GM analysis.

The CCQM activities have led to a better understanding of the need for guidance on the underlying traceability issues and the standardisation of GMO analysis. This has, in turn, raised the awareness of factors that can significantly impact upon the measurement uncertainty of a GM measurement result, and improved the knowledge on needs for standardisation and routes and means for establishing metrological traceability of GM analysis results. These scientific aspects have been fed into the stakeholders' community dealing with the implementation of EU legislation in terms of impacting upon the accuracy of labeling GM products thereby facilitating the further harmonisation and controls in global trade of GMO products.

D) Impact of CCQM Activities in the Energy Area

Case Study 8: International Equivalence, Accuracy and Traceability for Natural Gas Composition and International Trade

Global gas demand was estimated at 3 284 billion cubic metres in 2010, 7.4% up from the 2009 levels. Gas demand has increased by around 800 billion cubic metres over the last decade, or 2.7% per year. Gas has a 21% share in the global primary energy mix, behind oil and coal. For comparison, 50 billion cubic meters of natural gas is roughly equivalent to 7% of the US's consumption in 2010, or France's entire annual consumption in 2010.

Natural gas composition can vary from region to region and also vary on a daily and seasonal basis. The composition of natural gas with its associated measurement uncertainty is commonly used for the calculation of its calorific value, which determines its economic value in international and domestic trade. The international benchmark for the sale of natural gas is that the calorific value has to be specified within 0.1 per cent of the true calorific value. Meeting this benchmark is a significant measurement challenge, and has driven the development of natural gas composition measurement standards provided by several NMIs, allowing trade in natural gas with greatly reduced financial risks through accurate measurements of energy content. The international equivalence of natural gas measurement standards has been demonstrated in comparisons coordinated by the CCQM [**CCQM-K1,e,f,g** (1996); **CCQM-K16.a,b** (2001); and **CCQM-K23.a,b** (2004/2005)]. Future comparisons will support the diversification of energy gases such as biogas, shale gas, and hydrogen.

E) Impact of CCQM Activities in Advanced Manufacturing

Case Study 9: International Equivalence, Accuracy and Traceability in support of the International Technology Roadmap for Semiconductors

The International Technology Roadmap for Semiconductors, known as the ITRS, is the fifteen-year assessment of the semiconductor industry's future technology requirements. These future requirements drive present-day strategies for world-wide research and development among manufacturers' research facilities, and define future metrology needs. As the number of transistors per chip increases, the total chip size has to be contained within practical and affordable limits. This can be achieved by a continuous downscaling of the critical dimensions in the integrated circuit, which can be expressed in terms of Moore's Law as a scaling by a factor of 0.7 (½√2) every 2 years. Key metrologies for the 32 nm technical node device (ITRS, 2013) require capabilities for valid measurement of, amongst others, the thickness and chemical composition of gate oxides of < 0.5 nm thickness on silicon. This has led to industry requirements for traceable, repeatable and reproducible measurement methods. The most often used methods in Surface Micro/Nano Analysis (Secondary Ion Mass Spectrometry (SIMS), Auger Electron Spectroscopy (AES) and X-ray Photoelectron Spectroscopy (XPS), enable lateral nano-analysis as well as in-depth resolution at the nano-scale. The development of methodologies to enable traceable measurement results with these methods was undertaken by the CCQM Surface Analytical Working Group (SAWG), with the organization of the study **CCQM-P38**. This pilot study allowed to successfully establish a mutual calibration method for traceable ultra-thin silicon oxide films on Si measurement results by National Metrology Institutes using X-ray Reflectivity (XRR) and XPS. The subsequent **CCQM-K32** Key Comparison demonstrated that uncertainties at 95% confidence in the order of 0.05 nm could be achieved using traceable measurement results of ultra-thin silicon oxide films on Si. The results and expertise developed in the execution of **CCQM-P38** and **CCQM-K32** by NMIs have been used to develop the industry standard method ISO 14701:2011 (Surface chemical analysis -- X-ray photoelectron spectroscopy -- Measurement of silicon oxide thickness), which was published in 2011. The measurement capabilities at NMIs compared through CCQM-K32 address a core competency in the field of surface chemical analysis and are highly relevant for many other industrial “ultra thin film on substrate” systems. The measurement services and methods developed by NMIs through their participation in CCQM comparisons are now meeting the needs of industrial stakeholders for traceable measurement results that are in line with the ITRS requirements.

F) Impact of CCQM Activities on the redefinition of the units

Case Study 10: Chemical measurements for fundamental metrology

The establishment of isotope dilution inductively coupled plasma mass spectrometry (ID-ICP-MS) as the reference method of choice for a wide range of inorganic measurement applications has been a major achievement from the work of NMIs active in the Inorganic Analysis WG of the CCQM. Its performance has been developed and validated in initial comparisons (**CCQM-K2**: Cd and Pb in natural water) to the most recent such as (**CCQM-K**100: Copper in bioethanol). Furthermore, the CCQM has been active in developing comparisons to evaluate methods for the quantification of low level impurities for inorganic materials, including **CCQM-P62**: Trace analysis of high purity nickel and and **CCQM-K72: Purity of Zn**. Measurement capabilities, based on these methodologies, are now key for the determination of the molar mass and, hence, the chemical as well as the isotopic purity of ^{28}Si and required for the redetermination of the Avogadro constant N_A.

A critical factor for the redefinition of the SI units is the redetermination of the Avogadro constant N_A, which has been led by the International Avogadro Coordination (IAC), publishing[11] in 2011 a value of N_A with $u_{rel}(N_A) = 3 \cdot 10^{-8}$ [1]. Their approach is based on “counting” the atoms in a chemically ultra-pure, almost perfect single crystal of silicon enriched in ^{28}Si ($x(^{28}\text{Si}) > 0.9999$ mol/mol), for which the determination of the molar mass and the purity of ^{28}Si is of central importance.

Progress on these measurements was presented at the joint meeting of the CCQM WGs in November 2011 and the CCQM Workshop on the redefinition of the mole in April 2012. The determination of the molar mass of the silicon requires accurate isotope ratio measurements, which have recently been performed using inductively coupled plasma mass spectrometry (ICPMS) with solutions of Si dissolved in alkaline solutions, and successfully applied using a modified isotope dilution mass spectrometry (IDMS) technique in combination with several other methodological and experimental methods ending up in an uncertainty of the molar mass of ‘Si28’ of $u_{rel}(M) < 1 \times 10^{-8}$.

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[11] Andreas, B.; Azuma, Y.; Bartl, G.; Becker, P.; Bettin, H.; Borys, M.; Busch, I.; Gray, M.; Fuchs, P.; Fujii, K.; Fujimoto, H.; Kessler, E.; Krumrey, M.; Kuetgens, U.; Kuramoto, N.; Mana, G.; Manson, P.; Massa, E.; Mizushima, S.; Nicolaus, A.; Picard, P.; Pramann, A.; Rienitz, O.; Schiel, D.; Valkiers, S.; Waseda, A.: Determination of the Avogadro constant by counting the atoms in a ^{28}Si crystal. Physical Review Letters: 106 (2011), 3