Bureau International des Poids et Mesures

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

Report of the 25th meeting
(11-12 April 2019)
to the International Committee for Weights and Measures

Comité international des poids et mesures

LIST OF MEMBERS OF THE CONSULTATIVE COMMITTEE FOR AMOUNT OF SUBSTANCE: METROLOGY IN CHEMISTRY AND BIOLOGY

as of 11 April 2019

President (Outgoing)

Dr W.E. May, former member of the International Committee for Weights and Measures

President (Incoming)

Dr S.-R. Park, member of the International Committee for Weights and Measures also

Korea Research Institute of Standards and Science [KRISS], Daejeon

Executive Secretary

Dr R. Wielgosz, International Bureau of Weights and Measures [BIPM], Sèvres.

Members

Centro Nacional de Metrología [CENAM], Querétaro.

D.I. Mendeleyev Institute for Metrology, Rosstandart [VNIIM], St Petersburg.

Danish Fundamental Metrology Ltd [DFM], Hørsholm.

Federal Institute for Materials Research and Testing/Bundesanstalt für Material-forschung und –prüfung [BAM] Berlin.

Federal Office of Metrology METAS [METAS], Bern-Wabern.

Health Sciences Authority [HSA], Singapore.

Instituto Nacional de Metrologia, Qualidade e Tecnologia [INMETRO], Rio de Janeiro.

Istituto Nazionale di Ricerca Metrologica [INRIM], Turin.

Korea Research Institute of Standards and Science [KRISS], Daejeon.

Laboratoire National de Métrologie et d'Essais [LNE], Paris.

LGC Ltd [LGC], Teddington.

National Institute of Metrology [NIM], Beijing.

National Institute of Metrology (Thailand) [NIMT], Pathumthani

National Institute of Standards and Technology [NIST], Gaithersburg.

National Measurement Institute, Australia [NMIA], Lindfield.

National Metrology Institute of Japan, AIST [NMIJ/AIST], Tsukuba.

National Metrology Institute of South Africa [NMISA], Pretoria.

National Metrology Institute of Turkey [UME], Gebze-Kocaeli.

National Physical Laboratory [NPL], Teddington.

National Research Council of Canada [NRC], Ottawa.

Physikalisch-Technische Bundesanstalt [PTB], Braunschweig.

RISE Research Institute of Sweden AB [RISE], Borås.

Slovak Institute of Metrology/Slovenský Metrologický Ústav [SMU], Bratislava.

VSL B.V. [VSL], Delft.

The Director of the International Bureau of Weights and Measures [BIPM], Sèvres.

Observers

Agency for Science, Technology and Research [NMC, A*STAR], Singapore.

All-Russian Scientific Research Institute of Physical Technical Measurements, Rosstandart [VNIIFTRI], Moscow

Bulgarian Institute of Metrology [BIM], Sofia.

Central Office of Measures [GUM], Warsaw.

Centro Español de Metrología [CEM], Madrid.

CSIR National Physical Laboratory of India [NPLI], New Delhi.

Government Office of the Capital City Budapest [BFKH], Budapest.

Hong Kong Government Laboratory [GLHK], Kowloon.

Instituto Português da Qualidade [IPQ], Caparica

Kenya Bureau of Standards [KEBS], Nairobi

National Physical Laboratory of Israel [INPL], Jerusalem.

Liaisons

Cooperation on International Traceability in Analytical Chemistry [CITAC], Trappes.

European Commission – Joint Research Centre [JRC-Geel], Geel

International Atomic Energy Agency [IAEA], Vienna.

International Federation of Clinical Chemistry and Laboratory Medicine [IFCC], Milan.

International Organization for Standardization, Committee on Reference Materials [ISO REMCO], Geneva.

International Union of Pure and Applied Chemistry [IUPAC].

1. OPENING OF THE MEETING

The Consultative Committee for Amount of Substance: Metrology in Chemistry and Biology (CCQM) held its twenty fifth meeting at the International Bureau of Weights of Measures (BIPM), at Sèvres on 11-12 April 2019.

The following were present: H. Andres (METAS), J. Braybrook (LGC), A. Botha (NMISA, also ISO/REMCO), P. Brewer (NPL), R.J.C. Brown (NPL), S.Z. Can (UME), V.S. Da Cunha (INMETRO), L. Deleebeeck (DFM), C. Divieto (INRIM), P. Fisicaro (LNE), T. Fujimoto (NMIJ/AIST), B. Garrido (INMETRO), C. Gonzalez (NIST), B. Güttler (PTB), C. Haraldsson (RISE), K. Inagaki (NMIJ/AIST), J.S. Kim (KRISS), S.K. Kim (KRISS), Y. Kustikov (VNIIM), T.K. Lee (HSA), M. Lewin (NMIA), H. Li (NIM), K. Lippa (NIST), L. Ma (NIM), L. Mackay (NMIA), M. Máriássy (SMU), S. Marbumrung (NIMT), W.E. May (President of the CCQM), J. Melanson (NRC), Z. Mester (NRC and IUPAC), G. O'Connor (PTB), U. Panne (BAM), S.R. Park (President of the CCQM/CIPM/KRISS), H. Parkes (LGC), P. Phukphatthanachai (NIMT), O. Rienitz (PTB), A.M. Rossi (INRIM), M. Sega (INRIM, also CITAC), R. Stosch (PTB), A. Takatsu (NMIJ/AIST), T.L. Teo (HSA), W. Unger (BAM), A. van der Veen (VSL), S. Vaslin-Reimann (LNE), M. Winchester (NIST).

Observers: F. Dias (IPQ), V. Dobrovolskiy (VNIIFTRI), J. Dumanska (GUM), T. Fernández Vicente (CEM), I. Mugenya (KEBS), Z.N. Nagyné Szilágyi (BFKH), N. Oganyan (VNIIFTRI), M. Pakiela (GUM), C. Sánchez Blaya (CEM).

Liaisons: A. Fajgelj (IAEA), P. Gillery (IFCC), H. Morris (IFCC).

Representatives from Member State invited to attend as Observer: A.R. Alaskar (SASO-NMCC), G. Carroll (SL), S. Chaieb (INRAP), P.A. Gatti (INTI), O. Levbarg (SE "Ukrmetrteststandard") L. Morales Erazo (INM Colombia), R. Pérez Zambra (LATU).

Invited: S. Ellison (LGC / rapporteur), H. Emons (JRC-Geel), L. Érard (former CIPM member), R. Kaarls (Honorary CIPM Member), M. Kuehne (PTB), E. Kulyabina (VNIIMS), J.E. Lee (KRISS), E. Lin (NIST MML), G. Miller (ICHCLR), Y. Mitani, J. Morrow (NIST), T. Quinn (BIPM Emeritus Director), W. Richter, M. Sargent, H.G. Semerjian, R. Sturgeon (NRC).

Also present: S. Bergstrand (JCRB Executive Secretary), R. Josephs (BIPM), S. Maniguet (BIPM), P. Moussay (BIPM), M.J.T Milton (Director of the BIPM), S. Picard (BIPM / KCDB Coordinator), R. Wielgosz (BIPM / Executive Secretary of the CCQM), S. Westwood (BIPM).

Sent regrets: P. Thompson (NPL); Prof. Dr Leonid Konopelko (VNIIM), Dr D Sin (GLHK / KCWG Chair)

Dr W E May officially opened the meeting at 9:00 am on 11 April 2019. Dr May said that the meeting would include a reflection of the history of the CCQM, an update on present status and a look to the future. He welcomed two past BIPM Directors, Dr Kühne and Dr Quinn, who were present for this 25th meeting. He said the CCQM had become the global forum for progressing state-of-the-art in chemical and biological measurement. The early meetings had focused on fundamentals such as the idea of primary methods. It became apparent that chemical measurement was too complex to improve quickly by trying to match the complete hierarchical structure of physical measurement; there were many distinct measurands, present in a wide variety of complex matrices. The CCQM made rapid progress as working groups were formed to develop the best available measurement

methods for each area of work. Dr May read extracts from letters from: Dr W Louw, President of the CIPM, congratulating the CCQM on its achievements and noting that developments in the CCQM had positively influenced the work of other Consultative Committees; and Dr A Wallard, past Director of the BIPM, who congratulated the CCQM in rising to the challenge of raising the profile of metrological traceability in its field and developing a robust comparison programme to support this.

Dr May introduced the BIPM Director, Dr Milton; the Executive Secretary of the CCQM, Dr Wielgosz; Dr Kaarls the past President and "founding father" of the CCQM; and Dr S-R Park, incoming President of CCQM. He then invited participants to introduce themselves.

In his own introduction, Prof. H Morris (IFCC) took the opportunity to congratulate the CCQM on its contribution to measurement for healthcare, which, with other developments in metrology had made a positive and lasting difference to the practice of laboratory medicine.

1.1 Announcement of change in CCQM presidency (W.E. May)

Dr May announced that the CIPM had appointed Dr Sang-Ryoul Park, of KRISS, Republic of Korea, as the new President of the CCQM. The meeting welcomed Dr Park by acclaim.

1.2 Introductory remarks from incoming CCQM President (S-R. Park)

Dr Park said that as CCQM President, he was the sole CIPM member with a background in chemical and biological measurement, and in the future he hoped that more candidates from this community would be nominated for CIPM Membership. Recognizing the responsibility of his new role, he said that he looked forward to working with the many highly qualified and enthusiastic members of the CCQM. He thanked Dr Kaarls and his colleagues for laying the foundations for the CCQM's success. He noted that the CCQM had grown further under Dr May's leadership to become the premier network for advancing metrology in chemical and biological measurement. He recognized that the CCQM had already contributed greatly to the improvement of measurement and looked forward to the future fruits of the CCQM's endeavours. The success and growth of the CCQM meant that this was an ideal time to reexamine its role, build consensus on the goals of the unique network that is the CCQM, and reaffirm short-term and long-term outputs.

2. APPOINTMENT OF A RAPPORTEUR

Dr May invited Dr S Ellison to act as the rapporteur for the meeting and to continue in this capacity for 2019 and 2020. Dr Ellison agreed.

Dr Wielgosz thanked Dr Melanson for undertaking the role of Rapporteur for 2017 and 2018.

3. APPROVAL OF THE AGENDA

The President reviewed the proposed agenda, which was adopted without change.

4. OPENING REMARKS OF THE CCQM PRESIDENTS AND ACTIONS FROM THE 24TH MEETING OF THE CCQM

4.1 Opening remarks of the Presidents of the CCQM

Dr May noted that there was a good deal of business at this celebratory meeting and asked that presenters respect time constraints.

4.2 Actions and decisions of the 24th meeting of CCQM

Dr Wielgosz reported that the presentations from the previous day's workshop had been successfully made available for viewing online.

Turning to the decisions and actions of the 24th meeting of CCQM, Dr Wielgosz reviewed each of the actions and decisions and reported that all outstanding actions from the 24th meeting of the CCQM were complete.

It was noted that decision 12 required development of a policy for making reports accessible on the BIPM website to enable CMC review. Dr Wielgosz would verify that this had been included in the CCQM guidance documentation with the Chair of the CCQM Working Group on Key Comparisons and CMC Quality (CCQM-KCWG).

The meeting further noted that the CCQM proposal to form a Working Group on isotope ratio measurements, with Dr Mester as the first Chair, had been approved by the CIPM at its June 2018 meeting. The President welcomed Dr Mester to his new role.

Dr May proposed adoption of the report of the 24th meeting. The report was approved without change.

5. THE IMPACT OF CCQM ACTIVITIES (H. SEMERJIAN AND M. MILTON)

Dr H Semerjian (former Director, NIST)

Dr Semerjian recalled the history of BIPM, beginning with the signing of the Metre Convention in 1875. He noted, however, that chemical measurement did not receive the attention of the CIPM until almost a century after the signing of the Treaty. He observed that the post of Government Chemist had been established in the UK in 1852 to examine tobacco; that BAM had been formed to improve metallurgy in weapons, and that NIST had started to produce reference materials for a range of chemical problems. The mole was adopted as a base unit in 1971 at the recommendation of IUPAC. The CCQM itself had not been formed until 1995, after a great deal of work from NMIs with strong activities in chemistry. Dr Lyons, then NIST Director, was the Chair of the CIPM Working Group on Metrology in Chemistry that had preceded the CCQM and had recommended its establishment. Dr Kaarls was the first President of the CCQM.

Dr Semerjian reviewed examples of the international impact of chemical measurement. In particular, he drew attention to the measurement needs of the Organisation for Prohibition of Chemical Weapons (OPCW), and the climate research, which had led to the Montreal Protocol for restricting refrigerants. Economic impact studies at NIST had also established the considerable economic impact of chemical measurements.

The CCQM first met in 1995. The inaugural meeting had included about 25 individuals representing 13 organizations (12 being NMIs). Early work had turned to comparisons of capability; the need to

retain records of these comparisons eventually led to the establishment of the BIPM key comparison database (KCDB). Activity within the CCQM grew rapidly, stimulated further by the CIPM Mutual Recognition Arrangement (MRA) signed in 1999; this led to increased focus on comparisons and a consequent rapid increase in the number and scale of metrology comparisons in chemical and biological measurement, and the establishment of a Chemical Metrology Department at the BIPM.

Dr Semerjian described the expansion of chemical metrology around the globe. Considerable developments in the RMOs had led to over 6 000 CMCs for chemical measurement, supported by a range of comparisons.

Dr Semerjian noted that many areas were still growing in importance, including healthcare, energy, food safety, environmental monitoring and protection, industry and forensic science. The CCQM had undertaken comparisons and made significant impact in all of these areas. He provided examples of successful comparisons in healthcare, beginning with CCQM-K6, on cholesterol, in 2001. He recalled the formation of the JCTLM in 2002, which supported metrological traceability in laboratory medicine. The CCQM had contributed to environmental standards by, for example, establishment of an international comparison programme for ozone standards at the BIPM, and a working agreement between the BIPM and the World Meteorology Organization (WMO). He presented examples showing the considerable improvements in "greenhouse gas" measurement resulting from the work of the CCQM. He listed CCQM key comparisons on contaminants and nutritional components of foods and cited the CCQM's rapid response to the appearance of the contaminant melamine in milk powder, quickly arranging comparisons to support accurate measurement of melamine. He drew attention to the development of reference materials supporting the semiconductor industry, supported (for example) by CCQM-K157, which studied HfO_2 in thin films.

Dr Semerjian noted the CCQM's response to measurement needs. Working groups had been added as needed, and the early Working Group on Biological Analysis had expanded into three separate working groups.

Dr Semerjian concluded his address by thanking Dr Kaarls and Dr May for their untiring and devoted leadership of the CCQM, which had established a very firm foundation for the future, and by wishing Dr Park success in his new role.

Dr M Milton (Director, BIPM)

Dr Milton presented his reflections on the CCQM, based on his attendance at all of its meetings as well as those of many other CCs. He noted that the CCQM's work was primarily delivered through its working groups, which met more often than many other CCs. He felt that the regular reports from working groups to the CCQM plenary, and the effective challenges posed there, had been powerful drivers for progress.

He noted that unlike the reliance on regional metrology comparisons common in most physical measurements, the CCQM was able to centralize much of its activity leading to a larger number of CCQM rather than regional comparisons in chemistry as opposed to physics.

The CCQM was also supported by an effective laboratory programme at the BIPM, coordinating a substantial number of challenging key comparisons.

Dr Milton concluded by noting that there were now 59 States Parties to the Metre Convention and 42 Associates. This led to considerable global impact through mutual support for newer chemical metrology programmes. There was, however, more to do. At present, only 30 of the 59 Member States and six of the 42 Associate States held CMCs in chemistry. This showed that capacity building was an important and continuing role for the CCQM and BIPM.

6. REPORTS FROM THE CCQM WORKING GROUPS

6.1 Organic Analysis (CCQM-OAWG)

Dr L Mackay reported on past and present CCQM Working Group on Organic Analysis (CCQM-OAWG) activities. The WG was one of the first within the CCQM; its last meeting had 53 participants from 32 countries. Its activities began with the early implementation of isotope dilution mass spectrometry for the study of p-p DDE. A significant focus of the WG had been on the determination of the purity of pure calibration materials. It had coordinated a large number of comparisons for organic analytes in matrix materials, including the actual assessment of CRMs produced by institutes (known as Model 2 comparisons). It is currently coordinating its 50th key comparison.

Dr Mackay reminded the meeting of the OAWG terms of reference, which included organization of key comparisons and pilot studies to evaluate claimed capabilities for "higher order" measurement procedures for well-defined organic molecular entities, and to consider similar activities for high-priority method-dependent measurands.

Dr Mackay said that the 2018 OAWG mid-year meeting had been held in conjunction with the Protein and Peptide Therapeutics and Diagnostics Workshop (PPTD-2018) in Chengdu (China) and that this had been a good opportunity to interact with the clinical community in this important area. The 2019 interim meeting would also be accompanied by a technical workshop on "Advanced analytical technologies for life sciences".

Seven OAWG studies had been approved for equivalence since the previous CCQM meeting: CCQM-K78.a (amino acids in aqueous solution); CCQM-K131 (PAHs in organic solution); CCQM-K95.1 (PAHs in tea); CCQM-K109 (urea and uric acid in serum); CCQM-K141 (enrofloxacin and sulfadiazine in bovine muscle); CCQM-K142 (urea and uric acid in serum and plasma materials (a Model 2 comparison involving examination of participants' reference materials)), and CCQM-K138 (aflatoxins in fig).

Two comparisons were at the Draft B stage: CCQM-K147 (vitamin B3 in milk powder/infant formula) and APMP.QM-S11 (organochlorine pesticides in Ginseng root). Dr Mackay showed summary results for CCQM-K147; this was a further example of a Model 2 comparison with very good agreement for all of the CRMs that were assessed.

Two key comparison reports were at the Draft A stage. CCQM-K146 on polycyclic aromatic hydrocarbons in olive oil had provided good results, with a small number of institutes showing low values and this was under investigation. This had been coordinated in parallel with an Asia-Pacific proficiency testing programme for routine laboratories, with CCQM-K146 providing a benchmark to assess participants against. CCQM-K133/P170 for phthalates in PVC was a Track C comparison in an area that the WG had not carried out any previous key comparisons, for example, plastic materials.

CCQM-K148.a, on bisphenol A purity, the latest in the series of BIPM-coordinated purity comparisons, had recently returned measurement results. Dr Mackay showed a comparison of the draft results from CCQM-K148.a with those of CCQM-K55.a, completed in 2009; the recent results showed a strong improvement in agreement in terms of purity characterization.

CCQM-K154.a on zearalenone calibration solutions had recently returned results, which showed good agreement. This formed part of the BIPM capacity building programme for mycotoxin measurements. CCQM-K156 (PFAS/PFOA in ground water) was currently at the measurement stage.

Dr Mackay said that the OAWG had recently begun work on a more systematic way of assessing key comparison reference values, including the development of a flowchart giving guidance on data treatment. This had been trialed in recent comparisons. One of the aims was to include participants' uncertainty estimates in the KRCV values and thus to examine KCRV estimators that allowed this.

Dr Mackay reported that all OAWG CMCs for pure organics had recently been reviewed. This had provided an opportunity for institutes to consider submitting broader scope CMC claims. In conjunction with this, the group had prepared guidance on the requirements to underpin broad CMC claims.

In the planning of comparisons versus future needs, a previous survey of institutes' priorities had concluded that food safety and healthcare were the principal areas. This information was used to prioritize work in the ten-year plan for 'core competence' KCs.

Turning to future studies, Dr Mackay said that the OAWG sought approval for five key comparisons. Four of these formed part of their 10-year plan of Track A key comparisons. CCQM-K78.b on a non-polar multicomponent solution, coordinated by the BIPM and CCQM-K148.b on high-polarity pure organics, coordinated by the BIPM, are part of the planned KCs for calibration materials. Two future KCs were planned for matrix materials in the clinical area: CCQM-K159 on amino acids in plasma in 2019 and food safety: zearalenone in maize, representing high carbohydrate material in 2020. CCQM-K154.b on aflatoxin B1 in acetonitrile (in conjunction with the BIPM capacity building programme) was the proposed Track C comparison.

Dr May noted that these were consistent with the group's established programme. The meeting approved these comparisons.

6.2 Inorganic Analysis (CCQM-IAWG)

Dr M Sargent reported on past and current CCQM Working Group on Inorganic Analysis (CCQM-IAWG) activity. He reviewed the terms of reference of the group, which included the organization of key comparisons for a broad range of inorganic species; inter-laboratory work and pilot studies required to underpin the development of reference measurement systems; and to act as a forum for the exchange of information about the research and measurement service delivery programmes and other technical activities of the WG members.

Reviewing the history of the group, Dr Sargent noted that the inorganic field was one of the first topics to be covered by a comparison study in the CCQM; this had shown unexpected disagreement. Subsequent work had, however, improved quickly from that early base. CCQM-K2, for example, had shown agreement within 1 % for lead and cadmium in water at levels approximately 1 000 times lower than the first comparison.

Dr Sargent gave a brief overview of comparisons in progress. He drew attention to some comparisons in collaboration with the CCQM Working Group on Electrochemical Analysis (CCQM-EAWG), and to some 'stand-alone' pilot studies; one was on number concentration of gold nanoparticles.

Four key comparisons had been published since the last CCQM meeting: CCQM-K34:2016 on potassium hydrogen phthalate assay; CCQM-K128 and CCQM-P163 on heavy metals and organo-tin in leather powder; CCQM-K139 on elements in human serum; and CCQM-K149 on nitrogen in milk powder. Three more studies were at the draft B stage (CCQM-K142/P135.1, CCQM-K145/P183, CCQM-K143/P181), and one was at the draft A stage. Dr Sargent noted that the draft B reports involved over 20 separate measurands. Four further studies were currently out for measurement; a further three were at the planning and preparation stage. One of these (CCQM-K156/P200), involved

determination of strontium isotope ratio and would probably be transferred to the new CCQM Working Group on Isotope Ratios (CCQM-IRWG).

Proposals for three comparisons were presented:

- A key comparison and pilot study on selenoproteins in human serum;
- A key comparison and pilot study on anions in seawater; this was important to support current CMCs which were now based on relatively old KCs.

The meeting approved these proposed IAWG comparisons. Dr May reminded participants that comparisons always needed to be clear about the measurand, however participants should use the measurement methods they expected to use for delivery of services underpinned by CMCs.

Dr Sargent reported that an additional study, on non-metallic impurities (H, C, N, O, S) in high-purity metals, was important for industry. The study had been difficult to arrange, but looked increasingly feasible with support from NRC and CENAM. A proposal would be brought forward to a future meeting once feasibility has been established.

Dr Sargent then turned to future developments. The IAWG had been successful in understanding and reducing uncertainty in ICP-MS, developing isotope dilution mass spectrometry for high-accuracy measurement, and application of LC-ICP-MS to organometallic species. Developments in purity of elemental standards were making progress but needed further work. Three newer areas he foresaw as priorities were:

- Traceable and quantitative laser ablation ICP-MS elemental imaging;
- Protein measurement with ICP-MS of heteroatoms;
- Single particle ICP-MS for number concentration of nanoparticles.

Dr Sargent listed a number of important state-of-the-art pilot studies and noted that IAWG members regularly published papers in the area. A recent example, citing many previous papers, was a review of the role of ICP-MS in inorganic chemical metrology to be published in the forthcoming special issue of *Metrologia* on 'Advances in Metrology in Chemistry and Biology'.

Turning to stakeholder engagement, Dr Sargent said that the IAWG had established a practice of linking studies. For example, CCQM-P194 on nanoparticles in solution was in progress among NMIs and DIs, but the same material was being used in a parallel VAMAS study; the IAWG reference value would inform the VAMAS study.

In addition, stakeholders participated in joint IAWG-NMI workshops and there were a range of regional workshops.

In closing, Dr Sargent thanked all of the members of the IAWG since its formation, and the members of BIPM staff who had supported the group's work.

Dr Mackay asked whether the IAWG had compulsory comparisons, for example Track A comparisons, in which institutes were expected to participate. Dr Sargent replied that the IAWG undertook key comparisons to demonstrate capabilities, and he took the view that it was for the institutes to determine which capabilities they needed to underpin their services.

Ms Parkes noted that in the NAWG, studies generally took account of the type of methods likely to be used by participants, because this frequently dictated the nature of materials circulated. In consequence, the design studies often influenced the measurement method.

Dr Mester noted that the measurand for the nanoparticle counting study was number concentration, and asked whether CMCs for particle size could be supported by the study. Dr Sargent said that although this was not the focus of the present study, because particle count and element concentration could be determined, average particle size could in principle be determined. He felt, however, that this would require collaborative activity with other WGs, particularly the CCQM Working Group on Surface Analysis and potentially other CCs. Dr Wielgosz said that where there were topics of interest to other CCs, the topic should be referred through the CCQM Secretary, so that common interests could be identified and an appropriate referral made.

Dr Park encouraged the IAWG to engage with the CCQM Working Group on Protein Analysis in planning the proposed study on selenoproteins. Dr Sargent welcomed this suggestion.

6.3 Gas Analysis (CCQM-GAWG)

Dr Jin Seog Kim reported on the CCQM Working Group on Gas Analysis (CCQM-GAWG). The Working Group's focus was on composition of gaseous and gas/liquid mixtures. He said that the group generally worked with simpler matrices than other WGs and consequently benefited from a well-defined measurand with lower interference. Dr Kim said that the group had worked with chromatographic methods extensively, but spectroscopic methods were increasing in importance.

The WG worked extensively with RMOs, and with international bodies such as the WMO and IAEA, as GAWG members frequently provided reference values and materials for use in RMO linked studies.

The group now comprised 27 NMIs, and 56 individuals had been present at the April 2019 meeting. There had been 52 key comparisons and 22 pilot studies since its formation. Comparisons had started with simple binary mixtures and had increased in complexity to include automobile emission gases, natural gas and other complex gas mixtures. These supported environmental regulation, atmospheric monitoring and energy production.

Dr Kim gave an overview of comparisons across the group's history; he noted that there had been an increase in the number related to environmental monitoring.

Dr Kim said that three key comparisons had been approved since the last meeting: CCQM-K3.2019 (automotive gases), CCQM-K68.2019 (N_2O in air), and CCQM-K26b.2019 (SO_2). CCQM-K112 (biogases) was currently at the draft B stage and seven comparisons – CCQM-K150/P189 (particle count and charge conc.), CCQM-K137 (NO), CCQM-K41.2017 (H_2S), CCQM-K10.2018 (BTEX), CCQM-K118 (natural gas) and CCQM-K41.2017 (H_2S) were all at the draft A stage. CCQM-K117 (ammonia) and CCQM-K74.2018 (NO_2)/P172 (spectroscopy) were currently awaiting measurement results.

Dr Kim showed results for CCQM-K112 (biogas), in which one laboratory had used the Monte Carlo method of GUM Supplement 1 to evaluate uncertainty. Results showed generally good agreement with some laboratories relatively far from the reference value considering their reported uncertainties. He also presented results for CCQM-K137 which had shown one aberrant result; this had been removed, with the agreement of the WG, prior to KCRV calculation, which had now been agreed.

CCQM-K150/P189 was a particle counting study. The draft A report was in progress. Two institutes had identified measurement problems since the initial discussion; the draft A report was being updated to accommodate the removal of their values from the reference value calculation.

Dr Kim showed the three-year plan for future KCs and explained the rationale for some of the studies. He additionally gave some technical details of an agreed study (CCQM-P204) on CO_2 isotope ratio measurement, which was being coordinated by the BIPM and IAEA.

Dr Kim reported that the Scripps Institute had applied to participate in CCQM-K68.2019 as a pilot study participant, and the appropriate documentation would be completed and submitted to the CCQM President.

Two GAWG comparisons were proposed for approval:

- A key comparison on hydrogen purity; this would close a gap in current capability demonstration by addressing purity determination. Hydrogen was also important for future energy supply. Dr Kim confirmed that this would include determination of the mole fractions of seven impurities.
- A key comparison on dimethylsulphide in nitrogen at the nmol/mol level. This was important for meteorological and climate change modelling.

These studies were approved.

Summarizing activity in the past year, Dr Kim recalled the 39th and 40th meetings of the group, hosted by CENAM and the BIPM respectively. There were eight comparisons in progress, and six planned for 2019-2020. The next meeting would be in October 2019 at METAS (Switzerland); this would involve a joint meeting with the new CCQM Working Group on Isotope Ratios (CCQM-IRWG).

6.4 Isotope Ratio (CCQM-IRWG)

Dr Mester reported on the newly formed CCQM Working Group on Isotope Ratios (CCQM-IRWG).

The group had been formed because of the increasing importance of isotope ratio measurements in a range of applications. These included climate change, food provenance, doping control in sport, security and forensic science, authenticity and adulteration of pharmaceuticals and in 'big science' applications such as cosmology and planetary formation. These often depended on extremely accurate measurement of isotope ratio. Dr Mester also noted that many fundamental constants depended on isotope ratio characterization; the determination of Avogadro's constant by X-ray diffraction, or the realization of the triple point of water, were good examples. Deviations as small as one part in 10^5 were often important.

A task group had accordingly been formed by the CCQM to examine the need for a WG and this had first met in 2017. The task group had provided a comprehensive report to the CCQM in 2018, which had proposed the formation of a permanent Working Group. This had been accepted by the CCQM in 2018 and the CIPM had approved the formation of a new CCQM WG at their 2018 meeting.

Dr Mester reminded the meeting of the terms of reference of the group. These included:

- acting as an expert forum for development of isotope ratio metrology;
- coordination of key comparisons;
- development of a process to allow CCQM review of reference materials for isotope ratio measurement.

The first meeting of the group had been in Ottawa (Canada) in October 2018. This included a workshop with the CCQM-IAWG on mass spectrometry methods and other technical topics. The

meeting had also set out a framework for cooperation between the groups, and for close liaison with stakeholders. Preliminary comparison proposals had also been discussed.

The WG had also met on 7-8 April 2019. The meeting included technical presentations on the state of the art in isotope ratio measurement. Speakers had described systems for SI traceability of carbon isotope ratios, artefact-free isotope amount ratios, and calibration hierarchies for isotope ratio measurements in gases. Liaison updates had also been received from the forensic isotope ratio group FIRMS, from Euramet, from the Atomic Weight commission of IUPAC and from iRM-WG.

Two IRWG comparisons were proposed for CCQM approval:

- A pilot comparison on calibrated isotope ratio in natural copper, using three available test materials; this would require laboratories to apply all three of the most commonly used isotope fractionation correction methods to allow comparison between approaches.
- A key comparison on bulk carbon isotope ratio in vanillin, which supported determination of authenticity of natural vanillin, to be initiated in mid-2019.

These comparisons were approved.

A third pilot study, on CO_2 carbon isotope ratio in conjunction with the GAWG, had already been approved as CCQM-P204.

Dr Botha said that the April IRWG meeting had included robust discussions on the nature of the measurement claims supported by the studies and suggested that these statements could usefully be included in requests for approval for studies. Dr May confirmed that this was good practice for the CCQM.

Dr Botha asked for clarification on the group's review of reference materials. Dr Mester said that this would be considered in developing the procedures for review and would be discussed in conjunction with IUPAC, noting that the only metrological traceability exception in the CIPM MRA process was related to isotope ratios and their traceability to defined reference materials. Dr Fajgelj asked what methods could be used to compare reference materials; Dr Ellison noted that this type of comparative study had been undertaken on other types of material and was referred to as a Model 2 Key comparison.

6.5 Protein Analysis (CCQM-PAWG)

Dr J Melanson reported on behalf of the CCQM Working Group on Protein Analysis (CCQM-PAWG). He briefly reminded the meeting of the nature of proteins, which were the focus of the PAWG. The group originated from the earlier WG on Bioanalysis in 2015. Dr Melanson recalled the present terms of reference, which included demonstration of competence for measurement standards and capabilities for proteins and peptides, facilitation of global comparability of protein and peptide measurement results based on traceability to the SI, and acting as a forum for exchanging information on implementation of metrology in protein/peptide measurement among stakeholders.

Dr Melanson reported that, since the previous CCQM meeting, the group had met in China in 2018 and again in April 2019 at the BIPM.

Dr Melanson presented results from CCQM-K115.b/P55.2.b, on oxytocin purity. The results had, with one exception from a new NMI, shown excellent agreement across NMIs. The results were all well within 5 %, which compared well with earlier studies in the series and with capability elsewhere. Dr Melanson said that the principal challenge was identification and quantitation of impurities;

results for the individual impurities had also shown much improved agreement, though there still appeared to be room for further improvement.

Results from CCQM-K151/P191, a key comparison and pilot study on insulin P28d in solution, measured by amino acid analysis, had identified some sources of bias which could now be corrected. Dr Melanson showed results from CCQM-P164, on human growth hormone (HGH). This required participants to recover HGH quantitatively from the matrix as well as quantify the material and a 22kDa variant using peptide quantitation after digestion. Preliminary results were shown and again, comparability was very good.

A new study coordinated by the PTB was under way to determine total haemoglobin in blood. This was very time sensitive and some laboratories had received samples too late, requiring additional material to be sent.

The group proposed two new studies

- A key comparison on the catalytic activity of clinical enzymes in serum; six enzymes were currently under consideration but the study would involve a smaller number.
- A study on purity of parathyroid hormone (PTH) proposed by the BIPM and NIM, continuing the CCQM-K115 series.

In discussion of the proposals, Dr Wielgosz said that he was glad to see that the enzyme activity study was being developed in consultation with the coordinator of the IFCC-RELA scheme of inter-laboratory comparisons that had been underpinning the measurement capabilities of reference measurement laboratories for these measurands for years.

Ms Parkes noted that enzyme activity was invariably method-defined and asked whether it fell within the scope of the CCQM. Dr Wielgosz replied that the methods to be used were the IFCC reference methods, which were method defined and internationally accepted and met the criteria defined by the *ad hoc* CCQM WG on method defined measurands.

There were further questions on the type of material that would be used for the comparison, with remarks that lyophilized materials did not necessary provide direct confirmation of successful operation on patient samples. Dr Park said that lyophilized material was necessary for stability and Dr Emons added that commutability studies had been performed on these materials. Ms Parkes noted that enzyme study results would also be influenced by reconstitution of lyophilized materials. Dr Wielgosz observed that the IFCC were using similar samples in the RELA scheme and this did not appear to be a problem for those laboratories. Dr May added that issues with reconstitution would add to the challenge in the study.

In discussion of the PTH study, it was noted that the IFCC had been working on PTH for some time. In response, Dr May said that the study was intended to assess measurement capability but not clinical activity. Dr Wielgosz added that the IFCC had yet to certify a PTH material for purity and this work could contribute to such an activity. In response to a question, Dr Park confirmed that the material would be a suspension of ostensibly pure material, circulated solely with the object of testing capability for purity determination. It was also noted that the material was a recombinant protein. Dr Miller asked whether it would make more sense to start with a potential calibration material as the focus of any study. Dr Wielgosz replied that the proposed material was suitable as a model system assessing measurement capability for peptide purity determinations. Such a material could also later be a candidate for a primary reference material for PTH measurements, but this was not a matrix matched commutable calibrant, which would also be needed in the application of a calibration hierarchy to commercial kits. The IFCC representative said that a pure material of this kind would be

of benefit to clinical laboratories because no such material was currently available; this study would underpin capabilities for that purpose.

Following the discussion, the meeting approved both proposed studies.

Dr Melanson said that the working group proposed to nominate a PAWG representative on the KC Working group. Discussion of this point was deferred for consideration under the KCWG report.

6.6 Cell Analysis (CCQM-CAWG)

Dr J Morrow reported on the CCQM Working Group on Cell Analysis (CCQM-CAWG). The group had formed as a result of work in the working group on bioanalysis and the *ad hoc* microbiology steering group established in 2011.

The group's remit was i) to carry out key comparisons to evaluate "measurement services and capabilities including, but not limited to, the identification and quantification of cells and cell properties indicative of function as a result of emergent behavior in complex matrices and mixtures" and ii) "To identify and establish inter-laboratory work and pilot studies to enable global comparability of cell analytical measurement results through reference measurement systems".

Dr Morrow explained that this was a very large field. She said that microorganisms comprise two of the three domains of life (bacteria and archaea) and show great diversity developed over 3.8 billion years of evolution. In addition, there were many different types of cells forming different tissues in multicellular organisms. The CAWG domain therefore covered systems from single cells to complex systems of different cell types.

She drew attention to cooperation with ISO TC276, which had categorized the working space for cell measurements. This had been helpful to CAWG in delineating its own work. The group had developed a conceptual framework in which size, number (count) and (for future work) function and activity described the measurement space. At present the group was developing capability across the cell size/number space with minimal consideration of function or activity.

Dr Morrow showed the wide range of services currently delivered by different institutes. These included provision of reference materials for eukaryotic and prokaryotic cell systems and cell analogues; provision of reference data; calibration and measurement services such as cytometry and microscopy; reference value assignment for counts, cell adherence, concentration of (for example) CD4+, CD34+ and CD45+ cells; cell viability measurement and support for proficiency testing.

Turning to current activity, Dr Morrow reported that the October 2018 meeting had discussed potential study proposals and a review paper to be published shortly in a forthcoming *Metrologia* special edition. The April 2019 meeting had discussed ongoing and completed comparisons and had considered the need for new studies.

The report of CCQM-P165 (enumeration of CD34+ cells) was now complete. The report CCQM-P123 had yet to be completed but was expected to be delivered in October 2019. The extension would allow estimation of cell area from the study data on cell density and confluency (measures of area coverage), a potentially important outcome. Results from the study were shown; it appeared that cell area was influenced by the density of cells. This had implications for design of future studies. Reference values were intricate due to the complex study design; Dr Morrow thanked Dr Ellison and Dr Divieto for their work on this.

The CAWG proposed three new studies:

- A new pilot study, CCQM-P197, was proposed to assess capability to determine stem cell pluripotency on a structured nanoscale substrate. The study will use pluripotent stem cells from NIBSC and a coating material characterized at the NPL. Seeding density had been optimized to give a relatively straightforward counting challenge. The study will be run initially as a pilot; a key comparison was envisaged for the future.
- A pilot study (building on P165) would assess capability for enumeration of CD4+ and CD8+ cells. The group had discussed technical details of gating and an optimal strategy had been developed.
- A pilot study on quantitation of membrane intact E. coli in a water matrix. E. coli count was a common measurand in many countries, used as an indication of water quality. There were a range of methods, including plate counting, flow cytometry, 'most probable number' methods based on successive dilution, and qPCR. The aim of the study was to demonstrate global comparability, particularly using high accuracy flow cytometry or PCR methods. Seven institutes had so far contributed information on current methods. The study would be conducted in collaboration with the NAWG, allowing comparison of fundamentally different enumeration methods.

Ms Parkes confirmed that the E. coli study had been discussed by the NAWG and the measurand as originally proposed had been considered insufficiently defined for nucleic acid measurement. She said that participation by the NAWG would be optional for NAWG members. Dr Morrow noted that the measurand had been discussed in more detail following the NAWG comments, with the resulting restriction to membrane-intact *E. coli*. This was sufficient to define a clear measurand for nucleic acid measurement.

Dr May reminded the meeting that pilot studies were not being approved in the same way as key comparisons. The CAWG was accordingly free to progress with these three studies, however CCQM would need to continue to monitor the resources being devoted to pilot studies and may need to review the approval process of these going forward.

In closing, Dr Morrow noted that this was her final CCQM meeting as CAWG chair and thanked all the members of CAWG and CCQM for their support for the group's work

6.7 Nucleic Acid Analysis (CCQM-NAWG)

Ms Parkes reported on the activities of the CCQM Working Group on Nucleic Acid Analysis (CCQM-NAWG).

The group had emerged from the former working group on bioanalysis. Ms Parkes recalled the formation of the working group on bioanalysis, itself formed as a result of a task group led by Ms Parkes and Dr D Reeder. The first pilot study had used quantitative PCR. Results at that time were good by routine laboratory standards but covered an order of magnitude. Improvement was, however, rapid; CCQM-K61 showed that the range of results had reduced to approximately 10 %. Advances in technology, particularly the advent of 'digital' PCR (dPCR) backed up by orthogonal methods such as phosphorus determination at high DNA concentration, had established dPCR as a direct counting technology that could provide nucleic acid quantitation without recourse to calibration materials.

The scope of the present Nucleic Acid Working Group included chromosomes, DNA, RNA, methylation and other epigenetic modifications, messenger RNA and micro-RNAs in biological matrices. The group had established strategies for covering the measurement requirements in different sectors. For foods, the group used the AOAC "food triangle" which divided foods according to the proportion of major components. Studies had been conducted in most sectors of the diagram; a further study was proposed to cover the protein matrices. In the health area, studies focused on key genetic makers for clinical diagnosis. These particularly included markers for cancer susceptibility or markers directing appropriate treatment.

Ms Parkes said that the report for the key comparison CCQM-K86.c had been circulated to CCQM WG Chairs for final comment. The report circulated to CCQM WG Chairs had also been made available to the KCWG to support the review of related CMC claims. A number of observations had been made, and the April meeting of NAWG had reviewed comments and agreed actions on each. None of the remarks had affected assigned values or participant degrees of equivalence. The coordinators of the study would be addressing the comments in line with agreed actions and the report would be passed to the KCDB on completion.

Ms Parkes reported that the latest NAWG meeting had discussed a number of recent and ongoing studies. She summarized further work arising from the pilot study CCQM-P184. The study was intended to demonstrate detection and quantitation of mutations in a background of wild type DNA. The study had required participants to design their own probe sequences, providing a stringent test of complete assay development capability for new target sequences. Results on a sample using intact background DNA had demonstrated very good agreement for this very challenging measurement. However, one test material, for which the background "wild" type DNA originated from a sonicated sample, had shown an unexpectedly wide range of results. Follow-up studies by the coordinators (LGC and NMIA) had shown that this arose from a large proportion of short DNA fragments in the sonicated sample, in turn leading to differences in response depending on the length of the DNA probe sequences chosen by participants. Follow-up studies had been done to further elucidate reasons for dispersion; these had confirmed the probe length effect and additionally identified some sensitivity to reagent concentrations. As a result, the NAWG now had a greatly improved understanding of effects that might arise from some types of sample preparation for clinical samples.

Ms Parkes gave a brief update on progress on CCQM-P199, covering capability in low level detection and identification of a specific pathogen sequence. For this study, HIV-1 RNA copy number concentration was the measurand. There will be three study materials; two containing high and low levels of a synthetic gene fragment (HXB2) prepared by LGC and a third sample, prepared by NIBSC, containing inactivated HIV. Circulation of materials was expected in May 2019.

Turning to future studies, Ms Parkes said that the NAWG had considered a number of new key and pilot study proposals. These included

- A key and parallel pilot study on quantification (and fractional abundance) of genomic DNA extracted from a high protein matrix. This would support CMCs related to species quantitation in meat, fish and similar tissues, an economically important problem for authenticity and food safety. The group proposed to undertake measurement of inter-species gene fragment ratio as a key comparison, with pure materials for mass fraction calibration as a pilot study. The latter was important because much legislation was made in terms of ingredient mass fraction, and the addition of mass fraction would require participants to establish conversion factors to convert observed gene ratio to estimates of mass fraction.

- A study testing capability in methylation / epigenetics measurement (continuing the P94 series). Methylation is an important modification of DNA, affecting the expression of particular genes, and was an important diagnostic marker in some diseases. The NAWG proposed to focus on the ratio of methylated to unmethylated copies of a target sequence because individual copy number counts were adversely affected by the nucleic acid pre-treatment required for this measurand. A firm proposal was expected for a future meeting.

Ms Parkes asked for CCQM approval of the Key Comparison. On a proposal from Dr May, the meeting approved the study.

The NAWG had also discussed participation in the CAWG pilot study of E. coli enumeration, resulting in an improved measurand definition and agreement by several institutes to contribute nucleic acid results to the study.

In closing, Ms Parkes drew attention to the influence of NAWG members on standardization in ISO TC276 (biotechnology) and on the CCU drafting of the new SI brochure. These interventions established the validity of direct counting as a method providing SI traceable results for realizing nucleic acid copy number concentration.

Dr Mester asked whether the range of studies demonstrating dPCR measurement capability might allow the establishment of broad CMC claims based on dPCR. Ms Parkes confirmed that this was under consideration, although any CMC claim would still be subject to review.

6.8 Surface Analysis (CCQM-SAWG)

Dr W Unger reported on the CCQM Working Group on Surface Analysis (CCQM-SAWG) activity since the previous CCQM meeting.

The SAWG was established as an *ad hoc* working group in 2003 before being established as a permanent working group. The first comparison was in 2007. Dr Unger recalled the terms of reference for the group, which paralleled those of the CCQM itself, with a focus on spatially resolved chemical surface analysis at the micro- and nano-scale. The group also had a remit to act as a forum for exchange of information on research and development of surface analysis, establish contact with relevant stakeholders and promote the development of SI traceable chemical surface measurements. The group currently has participants from 18 institutes, although five had not sent participants to recent meetings.

Reporting progress on studies, Dr Unger said that CCQM-P190 (measurement of HfO_2 in thin film) had been completed, the subsequent CCQM-K157 is ongoing and that for CCQM-K153 (measurement of specific adsorption of N_2 and Kr on nonporous SiO_2 at liquid nitrogen temperature by BET) draft B was completed and distributed to CCQM WG chairpersons for approval.

Dr Unger reported that CCQM-K-153 had covered measurement of specific absorption of nitrogen or krypton on nonporous silica at liquid nitrogen temperature. This included an application of the BET method, a standard method for determination of surface area. This fitted into the ‘nonporous’ region of the SAWG measurement space, which also included microporous, mesoporous and macroporous regions. CCQM-K153 involved two measurands; amount of absorbed gas at liquid nitrogen temperature, expressed as specific absorption, and the BET surface area. Specific absorption results could in principle be traceable to the SI; BET was operationally defined. Five institutes participated. A detailed uncertainty budget was available for both measurands. Results had been excellent, with all laboratories agreeing well within their uncertainties and all in agreement with the reference value.

Reporting on CCQM-P190, Dr Unger described the study objective measurand (amount of substance of HfO_2 in a thin film), samples and methods. After showing transmission electron microscope images obtained in the study, he briefly reviewed the conclusions. The study identified a need to handle carbon contamination, harmonize the XPS measurement protocol, determine emission angle and identify a consensus value for attenuation length. These conclusions had informed the design of the ongoing CCQM-K157 study approved at the 24th Meeting of the CCQM.

The group planned a number of comparisons for the next three years:

2019: A pilot study on the amount of substance in a thin organic layer (previously approved).

2020: CCQMK-157, Measurement of the amount of substance of HfO_2; A key comparison on specific gas adsorption on microporous samples and a pilot study on homogeneous surface composition of an ionic liquid.

2021: A key comparison measuring the amount of substance in a thin organic layer.

Dr Unger additionally described a recently proposed pilot study to examine chemical composition in a deep nanoscale layer. This was important for the electronics industry and four participants had expressed an interest. The measurand will be the amount of $Ir(ppy)_2(acac)$ in a thin organic layer within an organic layer stack on a silicon substrate. He also reported that the SAWG had started work on characterization of graphene material grown by chemical vapour deposition (CVD). The work would examine coverage on the substrate, number of layers, level of disorder, uncertainty budgets associated with the measurement and data analysis. A link to VAMAS Technical Work Area 41 "Graphene and Related 2D Materials" would also be established.

Looking forward, Dr Unger said the group had established a task group on application of Raman spectroscopy. This had important applications but was currently seen as qualitative. He presented the terms of reference for the task group for approval by the CCQM.

Dr Unger reviewed the SAWG activities that have progressed the state of the art in measurement science. He listed the past and ongoing comparisons that had addressed new and challenging measurement problems, and drew attention to a number of key publications in surface analysis. He additionally described stakeholder engagement activities, including collaboration with VAMAS, input to ISO TC 201, contributions to Euramet projects, and contributions to two recent stakeholder workshops.

Dr Unger said that the SAWG was waiting on a CCQM decision on the method-defined measurand task group's report before deciding on studies for BET and any related CMC claims. Dependent on this, the group would be seeking approval for a key comparison on surface area for microporous samples, in order to complete coverage of the measurement space.

In discussion of the report, Dr Emons commented on the expression of amount of substance as a layer thickness; he suggested that the WG review the wording for this measurand. This initiated a discussion of appropriate measurands for surface analysis, which were often layer dimensions expressed as length. On a suggestion from Dr Milton, Dr Unger agreed that the wording for surface analysis measurands would be amended for consistency with past practice.

In closing, Dr Unger noted that this was his last meeting as SAWG Chair. He thanked the past and present CCQM Presidents, the CCQM Secretary, and all the staff at the BIPM who had supported the working group.

6.9 Electrochemical Analysis and Classical Methods (CCQM-EAWG)

Dr M Máriássy reported on the history and activities of the CCQM Working Group on Electrochemical Analysis (CCQM-EAWG). After presenting the current terms of reference, he recalled that the group started in 1998 as a working group on pH, later extended to refer to electrochemical analysis on the addition of conductivity interests. In 2017 the remit had been further expanded to include classical chemical methods. Dr W Richter had chaired the group from 1998-2002; Dr Máriássy had taken the Chair until April 2019.

The group had so far conducted 26 comparisons and 19 pilot studies, supporting 156 CMCs. He reviewed the study coordination effort, noting that while most studies had been coordinated by larger institutes it was good to see some new institutes acting as coordinator.

Two comparisons had been approved for equivalence since April 2018: CCQM-K18.2016 (pH of carbonate buffer) and CCQM-K34.2016 (assay of KHP). Two more studies were at the draft B stage CCQM-K152/P192 (assay of potassium iodate) and CCQM-P93 (pH CRM comparison). One Euramet comparison, with a link to EAWG, was at the measurement stage.

Dr Máriássy described progress on CCQM-K152, on assay of potassium iodate. The measurand was mass fraction of iodine; a secondary measurand was amount of oxidant expressed as potassium iodate. There had been some confusion arising from the status of results reported; Dr Máriássy confirmed that this would be resolved in line with CCQM policy, which prohibited change of status after measurement commenced. Preliminary results were good but showed large differences in uncertainty and some evidence of mutual inconsistency; these issues would be discussed and resolved where possible. The study also collected data on impurities which generally showed acceptable agreement.

CCQM-P93 studied capability for pH reference material production using a Model 2 design, in which participants submitted reference materials for assessment. The study used a differential method and a comparison solution to determine variation. Sixteen institutes registered; 15 submitted results. pH stability had been assessed, finding that the materials were stable within 0.0003 pH units or better over 8 months. Regression analysis had shown that all but one material showed consistent results within the declared uncertainties.

The comparisons CCQM-K34, a potassium hydrogen phthalate assay, and CCQM-K73.2018 on assay of HCl solution would be initiated during 2019. Dr Máriássy additionally showed a list of planned comparisons for 2020-2023.

Regarding stakeholder engagement, Dr Máriássy reported that EAWG members participated actively in ISO, IUPAC, OIML and other standards committees. He further reported that group members contributed to progress in the state of the art through technical presentations, showing three recent examples.

Dr Máriássy reported that the working group proposed a follow-up key comparison for pH measurement of a borate buffer, repeating CCQM-K19, an older study in order to underpin current CMC claims. In addition, a key comparison on oxalate assay was proposed for 2020, organized by NMIJ. This would extend existing capability. He asked for CCQM approval for these studies. The studies were approved.

In closing, Dr Máriássy noted that this was his final meeting as EAWG chair, and thanked members of the working group, fellow chairs, the CCQM Presidents and Executive Secretary and the BIPM staff for their support for the working group.

6.10 Key Comparison and CMC Quality (CCQM-KCWG)

Dr Botha (NMISA) reported on the activity of the CCQM Working Group on Key Comparisons and CMC Quality (CCQM-KCWG) on behalf of Dr Sin. After reminding the meeting of the terms of reference for the KCWG, she gave a brief history of the group. The present KCWG had been formed in 2003 from the CCQM Working Group on Key Comparisons, established in 1997. The first approved chemistry CMC claim had been published in the KCDB in May 2001; the group presently reviewed both chemistry and biology CMC submissions. For information, Dr Botha also showed the current membership of the KCWG, which included representatives from all regional metrology organizations (RMOs) as well as representatives from CCQM working groups and from the BIPM.

Dr Botha reminded the meeting of the CMC review process. RMO TC Chairs submit the RMO CMCs to the KCWG Chair in February of each year. The KCWG typically holds meetings on the weekend before the CCQM technical working group meetings in April at the BIPM. Review continues until all the outstanding matters are resolved, which typically takes eight to nine months. Formal approval of CMCs is done by the RMO TC Chairs on the Joint Committee of the Regional Metrology Organizations and the BIPM (JCRB) website.

Dr Botha reported that the CCQM now has over 6 200 chemistry and biology CMCs, about a quarter of all CMCs in the KCDB. The number of CMCs in the area continues to grow steadily, though there was a slight dip in 2017. In 2019, a total of 813 CMCs were submitted. She then gave a breakdown of chemistry and biological measurement CMCs by category as well as the number of key comparisons used to underpin these. She compared these figures to other Consultative Committees, noting that the CCQM underpinned the largest number of CMCs per key comparisons of any committee other than the CCTF.

Dr Botha briefly discussed some recent developments in CMC submissions. Use of the "core competence concept" had led to fewer comparisons at the expense of more time spent in planning and organization of "core" comparisons. Record or report cards, based on competence tables, had been developed by some CCQM WGs. There had been more broad-scope claims; this had shown that the KCWG needs more expert input in the review process to assess broad claims as they generally did not relate directly to single comparisons. Some examples of broad CMC claims were shown. The group was interested to learn more about the next implementation of the KCDB.

The KCWG was preparing for further CMC reviews, as many claims had been made before 2010. The group proposed to carry out reviews by service category; a provisional timetable for review was presented.

In closing, Dr Botha made a number of observations and recommendations for the attention of the CCQM. Observations included:

- Criteria were needed for making broad-claim CMCs;
- When moving towards wider scope CMC claims, the KCWG has to enlist more expert support in the review process;
- There was a need to examine the repeat frequency of KCs versus re-review frequency;
- The operation of the KCDB 2.0 in the CCQM inter-RMO review process had been discussed with the KCDB Coordinator and JCRB Executive Secretary. Dr Botha was happy that the processes foreseen in the KCDB 2.0 system would be adaptable to the processes being used in the inter-regional review in the KCWG.

The KCWG additionally offered a number of recommendations:

- Guidance documents on broad-scope CMCs must be available in open access to all NMIs/DIs in time for each CMC review cycle. It was suggested that any guidance be finalized at April WG meetings.
- It would be useful to clarify guidance on sources of traceability; specifically, Dr Botha asked whether there could be more than one source of traceability for one CMC, particularly in view of changes in Euramet membership.
- Guidance was needed on handling similar CMCs from more than one institute in a country.
- Requirements for purity assessment appeared to be different for the different technical WGs; it would be useful to discuss and share approaches with the KCWG.
- Owing to the emergence of broad-claim submissions for peptides and proteins, the KCWG will need the support of the PAWG on how to assess these claims technically.
- The NAWG suggested that the CCQM remind NMIs/DIs, via the RMOs, about their responsibility to regularly review their CMCs in line with new comparison evidence and other issues such as source of traceability.

In closing, Dr Botha thanked all the KCWG members, reviewers, and colleagues in the RMOs; and offered particular thanks to the supporting staff of the BIPM. Dr May additionally reminded the meeting that R Parris, of NIST, had also had a considerable role in setting out the present framework, both in developing the CMC review process and the activities of the KCWG.

Dr May invited discussions.

Dr Milton asked what guidance the KCWG was developing to ensure consistency of approach for broad-claim CMCs. Dr Botha said that this tended to depend on the 'working space' for each WG and consequently the KCWG relied heavily on transparency and discussion in the working groups.

Dr Milton asked about the distinction between 'deleted' and 'greyed out' CMC claims. The former were claims that the Institute had withdrawn permanently; 'greyed out' referred to CMCs that had been suspended pending further information or review. Following up, Dr Milton noted that some of these claims related to the change in status of the JRC, which had withdrawn from Euramet. Dr Milton asked, in general, whether a CMC should be suspended or removed if it relied on a historically valid reference material that could no longer be provided. Dr May pointed out that Euramet had issued an interpretation that made it clear that the CMC could stand within the RM's expiry date. Institutes had been advised, through the WGs, to review their CMCs.

Dr Park asked why there were so many CMCs deleted in Category 10. These were claims that NIST had chosen to remove.

Dr Semerjian asked about similar CMCs from more than one institute. He felt that this was contrary to the spirit of the CIPM MRA. Dr Botha said that, they had been confronted with the example of a number of institutes which has provided very similar but distinctCMCs. Dr Semerjian noted that this would arise in other countries with distributed systems and said that it should be for the country to determine which of the institutes was responsible for the particular service. Dr Güttler said that these distinctions often related to very different stakeholder groups and felt that some latitude was sensible. Dr May agreed.

Dr Semerjian noted that the growth of the CMC system had been remarkable and congratulated the KCWG on their work. He asked how other CCs were approaching CMC review. Dr Milton said that

some had been very stringent and were now moving to a less frequent review, backed up by evidence of institutes' quality systems to justify longer review periods.

Dr Braybrook asked whether the CMC database would allow analysis of usage. Dr Botha confirmed that this was expected.

6.11 *ad hoc* WG on the mole (CCQM-ah-WG-Mole)

Dr B Güttler gave a comprehensive review of the history of the CCQM *ad hoc* Working Group on the Mole (CCQM-ah-WG-Mole) and of the developments that led to the redefinition of the mole that will come into force in 2019. The WG had been tasked with preparation of a *mise en pratique* for the mole, development of the new definition and associated stakeholder engagement and promotion. Initially led by Dr Milton, Dr Güttler had taken over in 2015.

Dr Güttler attributed the earliest statement of the mole to Ostwald, in the 1893 edition of *Physiko-Chemische Messungen*. Since then, emergence of a consensus on atomic theory had led to the recognition of Avogadro's constant, and many textbooks identified the mole explicitly with number of particles. The new (from 2019) definitions for SI units are based on fundamental constants, with the definition of the mole based on Avogadro's constant. This required a fixed value for Avogadro's constant, in turn demanding an accurate measurement of the constant. Dr Güttler confirmed that this had been achieved by decades of work, which led to a value of the constant with a relative uncertainty better than 2×10^{-8}. The CCQM had contributed directly to this via key and pilot comparisons, particularly CCQM-P160 on the molar mass of ^{29}SI and CCQM-K32, on the amount of silicon oxide expressed as thickness of SiO_2 film on silicon.

Describing the evolution of wording for the 2019 definition of the mole, Dr Güttler noted the helpful advice of IUPAC, and the comprehensive consultation carried out between the CCQM and IUPAC. He completed the discussion by showing the agreed definition and drawing attention to its principal features.

Dr Güttler said that the group would now turn its attention to dissemination and promotion of the new definition and thanked the members of the working group for their considerable efforts to date. In response to a question from Dr Wielgosz, he said that he felt that it would be necessary to maintain the *ad hoc* working group for the time being, in particular to be able to answer any queries that arose after the new definitions came into force. This was reinforced by a comment from Dr Fajgelj, who said that he frequently encountered confusion between number of particles and amount of substance.

7. REPORT FROM CCQM TASK GROUP ON METHOD-DEFINED MEASURANDS

Dr Andres provided an update on the task group. He recalled the membership, which consists of himself, Dr Brown, Dr Ellison, Prof. Dr Emons, Dr Güttler,Prof. Li, Dr Mester, Dr Morrow, and Dr Wielgosz. He reminded the meeting of the principal aim of the group, which was to establish criteria used to decide which method-defined measurands and measurement services were in the scope of activities covered by the CCQM. He then drew attention to the final report of the task group, made available as paper CCQM/19-06 on the BIPM website. This gave a number of illustrative examples of method-defined measurands (also called operationally defined measurands in ISO

17034:2016), and provided criteria for CCQM use in determining whether an activity was within the scope of the CCQM.

Turning to the criteria, the task group report proposed that:

> "All the following requirements shall be met as agreed by consensus of the CCQM for method-defined measurands and measurement services to be considered in the scope of activities covered by the CCQM, and eligible for CMC claims in the BIPM KCDB:
>
> a. **The method-defined measurand must be within the remit of CCQM** (The remit of CCQM, as defined in its terms of reference)
>
> b. **The method-defined measurand must be internationally agreed and specifically defined in the field of application.**
> This demonstrates the global interest in the measurand and the need for international equivalence. Methods agreed only at a national or regional level are not acceptable.
>
> c. **The method-defined measurand must be a stable reference point in time.**
> References in the method shall be clearly defined and reproducible over time and not dependent on a specific (reference) material.
>
> d. **The method, as applied at the relevant NMI or DI, is considered as the highest metrological reference within a calibration hierarchy.**
> The NMI's or DI's measurement service shall disseminate metrological traceability. Routine test methods and data processing algorithms are out of scope.
>
> If a method-defined measurand and measurement service fails to meet the criteria, a narrower definition of the measurand that would pass the criteria is recommended."

The report proposed that these criteria be implemented on the decision of the present meeting.

Dr May congratulated Dr Anders on an excellent report and suggested that the report should be brought to the attention of other CCs. He invited a discussion of the report and its recommendations.

In relation to criterion b) Dr Güttler noted that the adoption of a method-defined CMC should not prevent development of improved methods that did not require operational definition. Dr Anders said that if this were achieved, criterion d) would come into play and the method-defined measurand would no longer meet all the criteria for CCQM business.

Dr Morrow thanked Dr Anders for his work and said that criteria c) and d) would be essential to the work of the CCQM Working Group on Cell Analysis (CCQM-CAWG).

Commenting on the principle of refining method-defined measurands until they met the criteria, Dr O'Connor said that refining method-defined measurands might make the resulting service irrelevant to the end users of the service. Dr Semerjian said that the criteria did not limit the services that NMIs were permitted to deliver; rather, it limited those that could reasonably be addressed by the CCQM.

Dr Winchester asked what the traceability requirements would be. Dr Anders replied that traceability was generally to the SI or other relevant references, via calibration for the conditions specified in the standard method.

Following the discussion, Dr May proposed adoption of the report and recommendations. This was agreed, with the reference to traceability criteria in d) modified to specifically indicate that this referred to metrological traceability as defined in the VIM and clarification in the example of pH measurement that in the 2002 IUPAC recommendation the possibility to achieve full SI traceability was described and achievable by adding an uncertainty for the Bates-Guggenheim convention. The approved report is available as CCQM/19-43.

Dr Anders further proposed that, since the work of the task group was now complete, the task group be dissolved. This was agreed.

Dr R Brown noted that a decision was still required on BET. Dr Unger said that this was also important to a comparison proposed by the surface analysis working group. Dr Unger agreed to review the criteria and lodge the request for approval for a KC including BET with the President.

8. BIPM PROGRAMME ON METROLOGY IN CHEMISTRY

8.1 Review of the BIPM Chemistry programme

Dr Wielgosz reported on the work in the BIPM Chemistry Department, and in particular its role in coordinating CCQM comparisons, international liaisons and coordination activities including support for the JCTLM, and running laboratory-based capacity building and knowledge transfer projects. He noted that the number of BIPM staff had remained stable over the period, but that the department had hosted over 50 visiting scientists in the last five years from 23 different countries and all regions that are fully active in the CIPM MRA. Summarizing the outputs from the current 2016-2019 Work Programme, he reported that the department had coordinated 12 comparisons in the period which had enabled 214 participations of NMIs in these, published 19 comparison reports, hosted 40 visiting scientists, published 14 papers, contributed to 11 standards and guidelines and supported 13 committee meetings at the BIPM.

Parts of the work were partly funded by voluntary donations; Dr Wielgosz thanked the IFCC, which has made a substantial contribution to the funding of JCTLM activities.

The Chemistry Department had been established in 2000, five years after the first meeting of the CCQM, and in describing technical achievements Dr Wielgosz drew attention to the improvements in the state of the art of measurement science in the NMIs that had been demonstrated through some of the BIPM coordinated comparisons since that time. The first programme, started at the BIPM in 2000, was on ozone standards in collaboration with the NIST. As a result, a three-fold improvement in agreement in ozone standards had been achieved since 2002, and ozone absorption cross-section measurements were now six times more accurate. Measurements at the BIPM, achieved with the support of NMI visiting scientists, had contributed to the recent publication of a new consensus value for the ozone cross-section. He showed that CCQM-K120 had demonstrated a four-fold improvement in the agreement of CO_2 in air measurement standards since the last comparison that had been carried out ten years previously. The comparison had strengthened links between the NMI community and the WMO-GAW Central Calibration Laboratory for Greenhouse Gases, and a paper describing developments in the field on ‘SI traceability and scales for underpinning greenhouse gas monitoring’ had received a CITAC “best metrology paper” award this year. Improvements had also been made in the field of air quality standards, with the systematic biases in nitrogen monoxide standards due to impurities having been eliminated as demonstrated in the most recent key comparison in 2018, CCQM-K137. Indeed, the highly subscribed BIPM secondment training programme on FTIR, had

been established in response to requests for knowledge transfer on methods, demonstrated by the BIPM in these comparisons, for impurity quantification in reactive gases.

He also reported that the BIPM was coordinating a total of eight comparisons on behalf of the CCQM OAWG and PAWG on small organic primary reference materials and calibration solutions and peptide primary reference materials. The BIPM in collaboration with a number of NMIs was coordinator of the purity core comparisons designed by the PAWG. He described the clinical application of measurements of C-peptide in diabetes diagnostics, the model peptide used in the first PAWG peptide purity comparison, and how reference materials delivered by NMIs and supported by the key comparison were being used in calibration hierarchies for clinical measurements. A paper published in *Clinical Chemistry*[1] in 2017, in collaboration with NMIs and University groups had demonstrated how the application of such calibration hierarchies could improve the agreement of results in medical laboratories.

The CCQM-K55 and CCQM-K148 series of key comparisons coordinated by the BIPM have supported the development of an OAWG core comparison model for small organic primary reference materials and purity measurement capabilities. Dr Wielgosz noted the increasing use of quantitative NMR in these comparisons by NMIs, and how this was an important tool in delivering SI traceability for pure reference materials. He reported on the outputs of the NMIJ-BIPM collaborative project on qNMR, which had been supported by visiting scientists from five different NMIs. The project has delivered reference data, now published on the BIPM website, on the use of seven different internal standards for qNMR, which give a minimum of four viable signals in any of the most common solvents for NMR work. The reference documents were drafted to provide guidance to NMIs developing capabilities in this field. The BIPM and NMIJ were extending qNMR activities to fluorine and phosphorus, and BAM would also be sending a visiting scientist to assist with this later in 2019.

Dr Wielgosz also drew attention to the visiting scientist programme, information on which was available on the BIPM website.

He described the capacity building and knowledge transfer laboratory based projects that had started in this programme, notably the Metrology for Safe Food and Feed and Metrology for Clean Air Programmes. The former had focused on knowledge transfer on mycotoxin measurements and calibrants, in response to needs raised by AFRIMETS. The fourth project meeting had been held at the BIPM on 5 April 2019, with over twenty institutes now involved. The BIPM had concentrated on training programmes on the characterization and value assignment of mycotoxin calibration solutions on zearalenone, aflatoxin B1, deoxynivalenol and patulin with the support of NIM (China). Sixteen visiting scientists had participated in the project so far, and measurements on the first key comparison on mycotoxin calibration solutions (CCQM-K154.a, ZON in acetonitrile) had been completed, showing very good agreement, demonstrating the efficacy of the training programme, and support for new NMI measurement services. The next comparison would focus on aflatoxin B1, and a collaborative project with NRC (Canada) would allow the BIPM programme to additionally cover ochratoxin A.

New knowledge transfer projects were planned in the 2020-2023 BIPM Work Programme including: visiting scientist secondments on dynamic methods for air quality gas standards in collaboration with METAS (Switzerland); a Metrology for Laboratory Medicine project focusing on purity assignment

[1] Little R.R., Wielgosz R.I., Josephs R., Kinumi T., Takatsu A., Li H., Stein D., Burns C., Implementing a reference measurement system for C-peptide: Successes and lessons learned, Clin. Chem., 2017, 63(10), 1447-1456

methods for peptides such as HbA1C hexapeptide calibrators; extension of the Metrology for Safe Food and Feed project for knowledge transfer on drug primary reference material characterization methods, with tetracyclines used as model compounds.

Dr May invited discussion of the report. Dr Semerjian said that greenhouse gases were an important area; particularly the issue of methane leakage. He said that more accurate methane measurement was likely to be increasingly important and he was pleased to see the improvements in capability demonstrated by the BIPM. Dr Wielgosz said that a further comparison was planned in 2023 by the GAWG, and would be coordinated by the BIPM, and one goal would be to achieve a further two-fold improvement in agreement of standards that would harmonize the approach for global methane monitoring.

8.2 Metrology Summer School, Varenna 2019

Dr M Sega drew attention to the forthcoming Summer School on Metrology, to be held in Varenna in 2019. The Metrology Summer School is organized by the BIPM in collaboration with the Italian Physical Society. The School includes a core module on "Fundamental Metrology", covering issues such as realization of the base units, metrological traceability and measurement uncertainty; this is supplemented by a choice of two optional modules covering "Physical metrology" and "Quality of life". There is provision for a limited number of sponsored participants from Member States or Associates that have emerging metrology systems; details were available on the BIPM website.

In discussion, Dr Fajgelj asked about the intended audience. Dr Sega said that the course was aimed at young scientists from NMIs, PhD students or working metrologists wishing to improve their knowledge.

9. COMMENTS ON WRITTEN REPORTS FROM RMOS

All Regional Metrology Organizations (RMOs) had been invited to submit written reports on their activities. Available reports had been posted as CCQM documents well in advance of the meeting. Dr Wielgosz summarized each report briefly and invited comments and questions

There were no further comments or questions on the RMO reports.

10. REPORT FROM THE JCTLM

Prof. Ian Young, JCTLM Chair, presented the JCTLM report. He reviewed the rationale for traceability in laboratory medicine, which was important in order to provide accurate diagnostic measurements. As an example, he referred to cholesterol monitoring where statins were prescribed if the cholesterol/HDL ratio was high. He reviewed improvements in cholesterol measurement and noted that the effect of treatment had a substantial effect on death rates from coronary and circulatory disorders. Another analyte, parathyroid hormone (PTH), was used to guide treatment for kidney disease. Thresholds were set to determine treatment. Unfortunately, variation across test kits for PTH was sufficient to change decisions on treatment. The JCTLM had been formed in order to address issues arising from such differences in measurement results.

He reviewed the membership structure of the JCTLM, which included NMI representatives and stakeholders.

The JCTLM operated a database of reference materials and reference methods and services. Applications for inclusion in the database were reviewed according to a stringent process. The

database currently included 290 CRMs, 194 RMPs and 176 services delivered by about 13 institutes. It was noted that this still represented a small fraction of all clinical analytes.

The JCTLM also provided training materials and resources on traceability in clinical medicine; these could be freely accessed via the JCTLM website.

He reported the challenges that the JCTLM had to address, including extending listings beyond clinical chemistry. As a result, the JCTLM has been in contact with the International Council for Standardization in Haematology (ICSH), which had received a recommendation to join the JCTLM Executive Committee. A second challenge was to better coordinate activities, especially in the development of reference measurement systems. However, recent meetings with the NMIs gave him confidence that progress would also be made in this area.

Dr Park asked about the issue of existing listings. There are a number of older materials on the JCTLM site which may not be comparable to those listed more recently, particularly in regard to commutability. Prof. Young replied that the JCTLM had procedures for dealing with such eventualities, and any claim that a material did not meet its specifications or intended use would be treated by the appeals process and could result in a re-review of a material.

11. CC GOVERNANCE AND OPERATIONAL ISSUES

11.1 CCQM Member Applications

Dr Wielgosz reported that the BIPM had received two applications for CCQM membership, from INTI (Argentina) and from Ukrmetrteststandard (Ukraine).

O Levbarg gave a brief presentation on Ukrmetrteststandard. The organization had been active in gas standardization since the 1970s and provided established standards for the Ukraine. It was a member of COOMET and had participated in several regional metrology comparisons. The organization was active in ISO TC 158 (gas standards), ISO 193 (natural gas) and ISO REMCO. The institute was also a long-established contributor to Eurachem activities, particularly in the measurement uncertainty and traceability working group. In closing, Mr Levbarg said that he was appreciative of the support of COOMET and CITAC, and drew attention to a recent article on Ukrmetrteststandard in *CITAC news*. He looked forward to contributing actively to CCQM activities.

Dr Wielgosz said that BIPM would write to both organizations with any requests for further information and noted that the next opportunity for a formal decision on membership would be in October 2019.

Dr Park confirmed that he would establish a group comprised of CCQM Members to review the received applications and provide him with a report and recommendation on whether the institutes met the membership criteria for the Consultative Committee.

11.2 Open access CCQM and WG documents

Dr Wielgosz recalled that CCQM had agreed to make papers publicly available where it was reasonable to do so. CCQM reports, publications, and working papers had been made publicly available on the BIPM website where possible.

12. UPDATE ON THE BIPM KCDB 2.0

Dr S Picard gave an update on development of a new version of the KCDB. The work was initiated by a decision of the CGPM in 2014 recommending revision of the KCDB.

Apart from the database itself for which a new search engine is being implemented, the future KCDB facility includes a CMC platform with provision for user accounts supporting submission and review of CMCs. There will also be support for comparisons and access to statistics on CMCs and comparisons.

The implementation of the new database requires a migration of data from the current KCDB to a new relational database based on MySQL.

Dr Picard briefly described the proposed arrangements for the KCWG review in KCDB 2.0. These had been demonstrated to the KCWG in its April 2019 meeting; this had reassured the developers and the KCWG members that the implementation would suit the needs of the CCQM. One advantage was that review would be completed on the database rather than requiring collation and distribution of information by email. This would allow automatic publication of CMC claims if there was full agreement among online reviewers. CMCs could be approved without going to the KCWG if the RMOs approved them.

In discussion of the report, Dr May said that a great deal of effort had been put into the quality of the CMC database and he hoped that this would not be compromised for convenience. Dr Botha said that any automatic referrals would be directed to the KCWG chair for confirmation; the only difference would be that CMC claims with no referee comments would not be considered at meetings.

Turning to implementation, Dr Picard proposed the involvement of selected members of the CCQM in testing, to be invited in due course. There would then be a full transition. For a brief period, the current system would be suspended to allow for safe migration of data. Implementation in 2019 was envisaged.

In response to a question from Dr Braybrook, Dr Picard gave a demonstration of the new web page. General users would have access to news, statistics on CMCs and comparisons, and would be able to search the database for particular CMCs. Login would be required for review. She also confirmed that it would be possible to track usage in the normal way.

Dr Mackay asked if there had been any surveying of stakeholders on the new format as it was still very focused on metrology institutes' terminology. Dr Picard said this had not occurred.

Dr Mester asked whether there was a unique identifier for CMCs to allow citation. Dr Picard said that there was provision for unique identifiers provided by the institute, and that it would be possible to provide a stable URL for the CMC.

Dr Wielgosz asked whether KCDB 2.0 would be available to support the next CMC cycle. The developers were currently optimistic that the database would be available for the December cycle.

There was a brief discussion about access for public search engines. It was not likely that individual CMCs would be indexed on public search engines as access to individual lines was via search and filtering pages. The developers would, however, consider how public search engine indexing could best be facilitated.

13. COMMENTS ON WRITTEN REPORTS FROM INTERNATIONAL ORGANIZATIONS IN LIAISON WITH THE CCQM

13.1 International Atomic Energy Agency [IAEA]

A report had been submitted prior to the meeting and was available among the meeting papers. There were no questions or comments.

13.2 International Federation of Clinical Chemistry and Laboratory Medicine [IFCC] (with presentation)

Prof. H Morris, IFCC President, gave a presentation on IFCC activities.

The IFCC is a federation of 107 national societies and 41 corporate members representing more than 50 000 clinical laboratory specialists world-wide. Prof. Morris noted that Africa was currently poorly represented and one of the IFCC's tasks was to build capacity there. The IFCC's goal is to promote excellence in laboratory medicine for better healthcare world-wide.

Prof. Morris said that healthcare faced increasing challenges, including increasing patient expectations, growing rates of chronic diseases, an ageing population, increasing costs of medical advances and limited healthcare budgets. He felt that uniformity of good medical practice is the key to financially sustainable healthcare systems, and that accurate or comparable laboratory results were essential to allow clinicians to use international practice guidelines effectively. The IFCC scientific division accordingly worked to promote comparability of patient test results through the development of reference measurement systems and by harmonization activities.

The scientific division is organized by topic; for example, there are working groups on troponin-I, haemoglobin A2 and other important clinical analytes. These working groups have made significant advances in application of metrological principles. As an example, Prof. Morris said that standardization of cholesterol assays is saving $AU100 million p.a. for a population of 25 million people.

The IFCC strategic plan included two main strands: research into methods for measurement of the value of laboratory medicine, and development of a compendium of tools to allow clinical laboratory specialists to conduct such measurements. This would take advantage of close cooperation with the International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR). Technically, it would require extension into disciplines other than clinical chemistry, such as molecular biology, proteomics, immunology, pharmacology and haematology. The IFCC believes that a global approach is necessary and that this would involve close participation with partners such as the BIPM, NMIs, and the WHO, who were all directly involved in standardization, with regulators, with professional and scientific societies and with academia.

In closing, Prof. Morris drew attention to the IFCC website (http://www.ifcc.org) and congratulated the CCQM on its 25th anniversary.

Dr May invited questions. Dr Mackay asked whether there was scope for NMIs to join the IFCC. Prof. Morris said that this would be welcome, and that membership required a nomination from the national IFCC organization.

Ms Parkes noted that her experience on the IFCC committee for molecular diagnostics was that the IFCC were keen to welcome members from NMIs, and valued their expertise in metrology, validation and method development. Dr May confirmed this from his own experience.

13.3 European Commission Joint Research Centre [JRC]

No report had been received in time for the meeting.

13.4 International Union of Pure and Applied Chemistry [IUPAC] (with presentation)

Dr Mester, in his capacity as IUPAC Analytical Division President, gave a brief report on IUPAC activities. He said that one of the key activities was the work towards the redefinition of the mole, and drew attention to the critical review of the proposed definitions published by IUPAC in *Pure and Applied Chemistry* (2017), **89**, 951-981.

He commented that 2019 is the 150th anniversary of the periodic table and the International Year of the Periodic Table, as well as the 100th anniversary of the formation of IUPAC. He drew attention to an award for younger chemists (http://iupac.org/100/pt-of-chemist/), which celebrated contributions to chemistry; some CCQM participants had already been recognized and he invited further nominations.

IUPAC was working towards a revision of the IUPAC compendium of analytical terminology (the "Orange Book") which was now about to be published. This includes terminology changes to bring the IUPAC terminology closer to international metrology usage.

Dr Mester also drew attention to a number of projects, including a project on SI Value assignment of purity for organic materials which was due to be published in 2019. Other projects included an evaluation of analytical methods for nanomaterials, and a brochure on metrological traceability for chemistry.

For further detail, Dr Mester drew attention to the written report presented in advance of the CCQM meeting.

Dr Milton said that CIPM had instituted a new formal procedure for admitting and reviewing liaisons, and would be writing to IUPAC with a memorandum of understanding for signature by the IUPAC President. He said that this as an important relationship for the CIPM because of IUPAC's well established contribution to work on the redefinition of the mole.

13.5 ISO REMCO

A report had been submitted prior to the meeting and was available among the meeting papers. There were no questions or comments.

13.6 Cooperation on International Traceability in Analytical Chemistry [CITAC]

Dr M Sega reported that CITAC was meeting on 13 April, the day following the CCQM meetings. The meeting would commence with presentation of awards for "Best Metrology Papers". She listed the three papers recognized this year, all of which featured CCQM participants:

- Brewer J B, Brown RJC, Tarasova OA, Hall B, Rhoderick GC, Wielgosz RI, SI traceability and scales for underpinning atmospheric monitoring of greenhouse gases, *Metrologia*, 2018, **55**, S174–SS181.
- Nelson MA, Waters JF, Toman B, Lang BE, Rück A, Breitruck K, Obkircher M, Windust A, Lippa KA, A New Realization of SI for Organic Chemical Measurement: NIST PS1 Primary Standard for Quantitative NMR (Benzoic Acid), *Anal. Chem.*, 2018, **90**, 10510-10517.

- Melanson JE, Thibeault MP, Stocks BB, Leek DM, McRae G, Meija J, Purity assignment for peptide certified reference materials by combining qNMR and LC-MS/MS amino acid analysis results: application to angiotensin II, *Anal Bioanal Chem*., 2018, **410**, 6719-6731

The meeting congratulated the winners by acclaim.

14. ADDRESS FROM NEWLY-APPOINTED CCQM PRESIDENT

14.1 Appointment of CCQM WG Chairs

The CCQM had agreed to adopt fixed terms for working group chairs, and a number of WG Chairs were accordingly stepping down. Presentations were made by Dr May to all chairs and vice-chairs that had completed this current term and he thanked them for their contributions to the success of the activities of the Committee.

A list of responsibilities for WG chairs had been circulated and nominations for chairs of WGs received. Institutional support was confirmed. The President had selected chairs and informed candidates accordingly. The President, Dr Park, then announced the following appointments, effective from the present meeting:

Organic analysis WG	Dr L Mackay (NMIA), deputy Dr K Lippa, (NIST)
Gas analysis WG	Dr P Brewer (NPL), deputy Dr S Lee (KRISS)
Inorganic analysis WG	Dr M Winchester (NIST), deputy Dr P Fisicaro, (LNE)
Nucleic acids WG	Dr J Huggett (LGC), deputy Dr M Vonsky (VNIIM)
Surface analysis WG	Dr T Fujimoto (NMIJ), deputy Dr A Shard* (NPL)
Electrochemical analysis WG	Dr S Seitz (PTB), deputy Dr T Asakai (NMIJ)
Cellular analysis WG	Dr J Campbell (LGC), deputy Dr Boqiang Fu (NIM)
Protein analysis WG	Dr J Melanson (NRC), deputy Dr C. Swart** (PTB)
Isotope Ratio Metrology WG	Dr Z Mester (NRC), deputy Dr J Vogl (BAM)
Key comparison and CMC Quality WG	Dr D Sin (GHLHK), deputy Dr A Botha (NMISA)
Strategic planning WG	Dr S-R. Park (CCQM President)
ad hoc WG on the Mole	Dr B Güttler (PTB)

Dr Park then presented Dr R Kaarls with an award for his long and distinguished service to the CCQM.

Dr Park made a similar presentation was to Dr W E May, recognizing his distinguished service as President of the CCQM

(* appointment confirmed on 30 April 2019; ** appointment confirmed on 29 April 2019)

14.2 Dates for CCQM WG meetings to be held in second half of 2019

The meeting for the joint OAWG/NAWG/PAWG and CAWG was originally scheduled for 2-4 October 2019. However, for logistical reasons it was proposed that the meeting be moved to 25-27 September 2019. This was discussed. It was noted that 25 September was the date of the International Metrology Congress in Paris. It was accordingly agreed that the meeting would be held on **2-4 October 2019**.

Dr C. Divieto summarized arrangements for these meetings. A workshop on "Advanced technologies for the life sciences" was also proposed, to be held at the Politecnico di Torino. This would be open to CCQM members, academics and practicing clinicians.

Information on location of, and access to, Torino, was provided and would additionally be sent to participants on registration.

The next meeting of the GAWG would be held at METAS (Switzerland) from 8-9 October 2019, with a joint meeting of the IRWG on 10 October.

The IAWG would meet on 10-12 September 2019 at UNIIM in Ekaterinburg (Russian Federation).

For information, Dr Park added that KRISS had offered to hold the October 2020 meetings of a number CCQM WGs and he would ensure consultation on dates.

14.3 Date for next year's April CCQM meetings

The 26th meeting of the CCQM will be at BIPM on 23-24 April 2020

15. CLOSING REMARKS FROM THE OUTGOING CCQM PRESIDENT

Dr May addressed the meeting. He recalled his appointment as Director of NIST by President Obama in 2015, and his induction into the NIST Hall of Fame. He gave a brief outline of his education and career, and some examples of his early work in metrology, joining NIST (then known as NBS) in 1971. He noted that had served on the US National Commission on Forensic Science. He kindly attributed many of his professional successes to his close involvement in the international metrology activities of the CCQM and CIPM, both as Organic Analysis WG Chair and later as President of the CCQM.

He closed by thanking Dr Kaarls for his personal support at the CCQM and members of the CCQM. The meeting stood to applaud in recognition of Dr May's contribution to metrology and to the CCQM.

16. CLOSING CEREMONY

In the absence of any other business, the President of the CCQM, Dr Park, closed the meeting at 15:20 on 12 April 2019 and thanked participants for their contributions, reports and participation in the discussions. Dr Park further thanked the staff of the BIPM for their support in hosting the meeting and wished all attendees a safe journey home.

DECISIONS AND ACTIONS FROM THE 25TH MEETING OF THE CCQM

1. The CCQM approved the report of the 24th Meeting of the CCQM.
2. **Action**: KCWG Chair to ensure that a policy for making reports accessible on the BIPM website to enable CMC review is included in the updated CCQM KCWG guidance document
3. CCQM approved five Key Comparisons proposed by OAWG: CCQM-K78.b on a non-polar multicomponent solution; CCQM-K148.b on high polarity pure organics; a new Key Comparison on Zearalenone in Maize; CCQM-K154.b on aflatoxin B1 in acetonitrile and CCQM-K159 on amino acids in plasma.
4. CCQM approved a proposal for a Key comparison on hydrogen purity and a Key comparison on dimethylsulphide in nitrogen at the nmol/mol level, to be coordinated by the Gas Analysis Working Group.
5. CCQM approved proposals for a KC and parallel Pilot study on selenoproteins in human serum, and a KC and parallel Pilot study on anions in seawater, coordinated by the inorganic analysis working group.
6. CCQM approved proposals for a pilot comparison on calibrated isotope ratio in natural copper, and a Key comparison on bulk carbon isotope ratio in vanillin, to be coordinated by the Isotope Ratio Working Group.
7. CCQM approved proposals for two studies to be conducted by the protein analysis working group: A Key comparison on the catalytic concentration of clinical enzymes in serum and a Key Comparison on purity of parathyroid hormone (PTH), continuing the CCQM-K115 series.
8. CCQM approved proposals for three studies to be coordinated by the Nucleic Acid Working Group: A Key and parallel Pilot study on quantification (and fractional abundance) of genomic DNA extracted from a protein matrix, a Key Comparison on inter-species gene fragment ratio, with pure materials for mass fraction calibration as a parallel Pilot study, and a Pilot study testing capability in methylation / epigenetics measurement (continuing the CCQM-P94 series).
9. CCQM approved proposals for a follow-up key comparison for pH measurement of a borate buffer, repeating CCQM-K19, and a key comparison on oxalate assay, to be coordinated by the electrochemical analysis and classical methods working group.
10. The CCQM accepted the recommendations of the report of the Task Group on Method-defined measurands and adopted the criteria set out therein. The report will be made available on the CCQM website. (Completed, see CCQM/19-43)
11. Noting that the work of the Task Group on Method-defined measurands was complete, CCQM dissolved the task group.
12. **Action:** Dr Unger to review the criteria for method-defined measurands and provide a request for approval for a KC including BET to the CCQM President
13. **Action:** Dr Park to appointment a team of CCQM Members to review CCQM Member applications and provide him with recommendations.

14. The CCQM thanked Dr W E May, outgoing President of the CCQM, for his distinguished service

15. The CCQM President, Dr Park, announced the following WG Chair and Deputy appointments, effective from the present meeting:

Organic analysis WG	Dr L Mackay (NMIA), deputy Dr K Lippa, (NIST)
Gas analysis WG	Dr P Brewer (NPL), deputy Dr S Lee (KRISS)
Inorganic analysis WG	Dr M Winchester (NIST), deputy Dr P Fisicaro, (LNE)
Nucleic acids WG	Dr J Huggett (LGC), deputy Dr M Vonsky (VNIIM)
Surface analysis WG	Dr T Fujimoto (NMIJ), deputy Dr A Shard* (NPL)
Electrochemical analysis WG	Dr S Seitz (PTB), deputy Dr T Asakai (NMIJ)
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Protein analysis WG	Dr J Melanson (NRC), deputy Dr C. Swart** (PTB)
Isotope Ratio Metrology WG	Dr Z Mester (NRC), deputy Dr J Vogl (BAM)
Key comparison and CMC Quality WG	Dr D Sin (GHLHK), deputy Dr A Botha (NMISA)
Strategic planning WG	Dr S-R. Park (CCQM President)
ad-hoc WG on the Mole	Dr B Güttler (PTB, Germany)

(* appointment confirmed on 30 April 2019; ** appointment confirmed on 29 April 2019)

16. **Action**: The rapporteur, Dr Ellison to draft “Decisions and Actions” document and “Report of 25th Meeting of the CCQM”.