Bureau International des Poids et Mesures

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

Report of the 26th meeting
(26-28 April 2021)
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 26 APRIL 2021

President

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 Institute of Metrology METAS [METAS], Bern-Wabern.

Health Sciences Authority [HSA], Singapore.

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

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 Metrological Research/Istituto Nazionale di Ricerca Metrologica [INRIM], Turin.

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 /TÜBITAK Ulusal Metroloji Enstitüsü [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

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 Nacional de Tecnología Industrial [INTI], San Martín, Prov. Buenos Aires.

Instituto Português da Qualidade [IPQ], Caparica.

Kenya Bureau of Standards [KEBS], Nairobi.

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

National Physical Laboratory of Israel [INPL], Jerusalem.

State Enterprise "All-Ukrainian State Scientific and Production Center of Standardization, Metrology, Certification and Consumer' Rights Protection [SE "Ukrmetrteststandard"], Kiev

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 sixth meeting as an online meeting hosted by the International Bureau of Weights of Measures (BIPM), from 26 to 28 April 2021.

The following were present: M. Akgöz (UME), H. Andres (METAS), M. Arce Osuna (CENAM), M.d.R. Arvizu Torres (CENAM), H. Aslan (DFM), C. Augusto (INMETRO), Y.-K. Bae (KRISS), A. Botha (NMISA, also ISO/REMCO), J. Braybrook (LGC), P. Brewer (NPL), R.J.C. Brown (NPL), D. Burke (NMIA), S.Z. Can (UME), J. Carney (NIST), L. Deleebeeck (DFM), C. Divieto (INRIM), L. Dong (NIM), Z. Durisova (SMU), S. Ellison (LGC), M. Fernandes-Whaley (NMISA), P. Fisicaro (LNE), T. Fujimoto (NMIJ/AIST), B. Garrido (INMETRO), C. Gonzalez (NIST), B. Güttler (PTB), N. Hanari (NMIJ/AIST), C. Haraldsson (RISE), K. Inagaki (NMIJ/AIST), Y. Kustikov (VNIIM), S Lee (KRISS), K.-S. Lee (KRISS), H. Li (NIM), K. Lippa (NIST), L. Mackay (NMIA), M. Máriássy (SMU), J. Melanson (NRC), Z. Mester (NRC and IUPAC), G. O'Connor (PTB), U. Panne (BAM), S.R. Park (President of the CCQM/CIPM/KRISS), R. Paroli (NRC), M. Pérez Urquiza (CENAM), J. Pillay (NMISA), J. Rodrigues (INMETRO), A.M. Rossi (INRIM), M. Sega (INRIM), D. Smeulders (NMIA), E. Sobina (UNIIM), R. Stosch (PTB), T. Tarhan (UME), T.L. Teo (HSA), A. van der Veen (VSL), S. Vaslin-Reimann (LNE), J. Vogl (BAM), D. wang (NIM), C. Yafa (NIMT).

Observers: R. Chipanova (BIM), F. Dias (IPQ), V. Dobrovolskiy (VNIIFTRI), J. Dumanska (GUM), J. Fang (NMC, A*STAR), T. Fernández Vicente (CEM), P. A. Gatti (INTI), C. Ho (GLHK), F.M. Kai (NMC, A*STAR), O. Levbarg (SE "Ukrmetrteststandard"), Z.N. Nagyné Szilágyi (BFKH), N. Oganyan (VNIIFTRI), T. Okumu Oduor (KEBS), A. Petrenko (SE "Ukrmetrteststandard"), M.M. Puelles (INTI), H.K. Rotich (KEBS), D.W.M. Sin (GLHK), M. Strzelec (GUM).

Liaisons: P. Gillery (IFCC), M. Groening (IAEA).

Representatives from Member State invited to attend as Observer: D.A. Ahumada Forigua (INM Colombia), G. Carroll (SL), E. Ferreira (LATU).

Invited: A.R. Al Askar (SASO-NMCC), T. Asakai (NMIJ/AIST), J. Campbell (LGC), V.S. Da Cunha (INMETRO), B. Fu (NIM), J. Huggett (LGC), E. Kulyabina (VNIIMS), E. Lin (NIST MML), G. Miller (VCU), S. Seitz (PTB), A. Shard (NPL), C. Swart (PTB), M. Tarlov (NIST), M. Vonsky (VNIIM), M. Winchester (NIST).

Also present: R. Josephs (BIPM), S. Maniguet (BIPM), M.J.T Milton (Director of the BIPM), R. Wielgosz (BIPM / Executive Secretary of the CCQM), S. Westwood (BIPM), J. Viallon (BIPM).

1.1. Welcome

Dr S-R Park officially opened the meeting at 12:00 pm (CET) on 26 April 2021. The meeting was held online. Dr Park welcomed delegates from across the world, particularly thanking those who were attending at extreme local times. He noted the ongoing Covid-19 pandemic and wished all present continuing good health. He regretted the necessity to cancel the 2020 plenary meeting but was

pleased to see that many of the CCQM working groups had continued their work during the pandemic.

Dr Park invited participants to send, by email, any thoughts that could not be conveyed in person in the shorter online meeting format.

2. PRESENTATION OF LIST OF PARTICIPANTS AND RULES OF ORDER FOR ON-LINE MEETING

Dr Wielgosz shared a list of registered participants, which included 101 participants from 45 institutes.

Dr Wielgosz said that the meeting had been structured in order to maximize time for discussion and hoped that participants had been able to review the many meeting papers and presentations posted online on the newly restructured BIPM website. He provided brief guidance on use of the online meeting platform. He additionally noted that Dr Westwood and Dr Viallon (both currently at BIPM) would assist as moderators.

3. APPOINTMENT OF A RAPPORTEUR

Dr Wielgosz noted that Dr Ellison (LGC) had been appointed as Rapporteur for three years with effect from the 25th meeting. The meeting confirmed appointment of Dr Ellison as rapporteur.

4. APPROVAL OF THE AGENDA

Dr Wielgosz presented the proposed agenda, which was adopted without change.

5. OVERVIEW OF CCQM ACTIVITIES SINCE THE 25TH MEETING OF THE CCQM, APRIL 2019

Dr S-R. Park provided a summary of CCQM activities since the 25th meeting of the CCQM in April 2019). He recalled the celebration of the 25th meeting of CCQM in 2019 and the many leaders of CCQM up to 2019. Dr Park additionally thanked INRIM for hosting the interim CCQM-SPWG meeting in Torino in 2019.

Dr Park noted the subsequent rapid spread of Covid-19 world-wide and the adverse effect on CCQM

meetings, none of which could be held in person since the beginning of 2020. Despite this CCQM had held over 70 video conferences and meetings since April 2019, representing a great deal of activity. The meetings had progressed 40 comparisons, including two related to SARS-CoV-2, and had helped progress development of the CCQM strategy for 2021-2030

The period since April 2019 had seen some important technical activities. For example, in 2020, CCQM had recommended a value for the absorption cross-section of ozone, which would underpin world-wide ozone monitoring. This followed a CCQM workshop on the topic of ozone monitoring. The CCQM Working Group on Gas Analysis (CCQM-GAWG) had additionally formed task groups on greenhouse gas scale comparisons and on Ozone Cross-section.

CCQM had moved very quickly to support SARS-CoV-2 measurement response. Activity had included a pilot comparison, CCQM-P216, on Quantification of SARS-CoV-2 monoclonal antibody in solution (coordinated by NIM, NRC and BIPM) and another, CCQM-P199.b, on SARS-CoV-2 RNA copy number quantification, coordinated by LGC, NIMC, NIBSC, and NIST.

Further progress had been made on Broad Scope CMC claims. Dr Park said this was an important line of development and would increase the efficiency of work to support CMC claims in future.

Dr Park drew attention to the BIPM activities in Metrology in Chemistry and thanked BIPM for its continued work in coordinating CCQM key and pilot comparisons, as well as organizing and hosting 76 video conferences for the CCQM WG and CCQM Webinars on ‘Ensuring the reliability of measurements in response to the Covid-19 Pandemic’ during the period.

Further details of some of the activities are given in individual working group reports, below.

6. PANDEMIC RESPONSE CASE STUDY: CCQM-P199.B, SARS-COV-2 VIRAL RNA QUANTIFICATION WITH RT-DPCR

Dr J. Huggett (Chair, CCQM-NAWG) presented a summary of CCQM-P199.b, a study of SARS-CoV-2 viral RNA quantification with reverse transcription/digital PCR (RT-dPCR). He noted that there were currently two basic approaches to SARS-CoV-2 detection: detection of the viral genome, and detection of viral protein. He noted that the importance of these methods had greatly increased public awareness of PCR as a powerful method for diagnosis.

He addressed the detection of SARS-CoV-2 and requirements for accuracy, noting that the number of copies in ongoing infection was high (10^6 mL^{-1}) and the methods were highly sensitive. However, in practice the amount of viral RNA could be very much lower in field samples. Viral RNA concentration could be between 10 mL^{-1} and 10^{10} mL^{-1}. The dynamic range of methods also varied considerably, reducing sensitivity. In part as a result of this, detection capability for different methods appeared to vary over four orders of magnitude. Dr Huggett also noted that many estimates of detection capability were based on available test samples, few of which had been accurately quantified. More accurate measurement was accordingly needed to underpin assessments of capability in routine measurements.

Dr Huggett briefly described the principal of digital PCR. By comparison with traditional quantitative PCR, samples were diluted and dispersed among a large number of partitions (10^5 – 10^7 depending on

exact methodology) so that each partition contained (on average) less than one molecule. Counting of partitions showing amplification then gave a very accurate estimate of concentration, based on counting.

To demonstrate international capability the CCQM-P199.b comparison used four test materials; one purified high-concentration material and three gravimetrically prepared low-concentration samples. Sequences were provided but laboratories were expected to choose or develop their own assays. No calibrators were provided. The high concentration material included sufficient RNA to determine by conventional chemical methods.

Results of the comparison had been available in an exceptionally short time; six months from initiation of the study. Results showed a range of about ±40 %, a very considerable improvement over routine laboratory results which, in similar circumstances, would be unlikely to agree within orders of magnitude. In addition, results on the pure material from orthogonal (chemical) methods also showed good agreement, adding confidence in the combination of RNA transcription and amplification in dPCR.

In closing, Dr Huggett drew attention to a number of activities aimed at transferring this new capability, including the use of dPCR for assigning values to EQA (proficiency testing) samples.

Dr Huggett thanked LGC, NIM, NIST and NIBSC for coordinating the study, PTB and GBD for chemical measurements, and VNIIM, BIPM and KRISS for their support in managing and advising on study organization and processes. Discussion and questions followed. Dr Wielgosz asked how IVD manufacturers standardized their measurements before reference materials were available. Dr Huggett explained that a variety of methods were in use. Some used digital PCR, but with comparably little attention to metrological properties such as traceability and uncertainty

Dr Botha asked whether it was possible to produce certified matrix reference materials for virology. Dr Huggett replied that although he was not yet aware of any commercially available SARS-CoV-2 materials, but matrix materials were certainly available for other viral pathogens. In response to a further question, he added that CCQM members certainly had a role in underpinning measurements on such materials, both via capability development and by provision of traceable reference values.

Dr Gonzalez asked how reference materials for virology would help in the case of emergent variants. Dr Huggett replied that the capability could be quickly adapted as variants emerged.

Dr Andres asked which orthogonal methods had been applied. Dr Huggett said these included the molecular counting method developed at KRISS and chemical measurement of (for example) phosphorus. Dr Park added that the KRISS method could in principle be sequence-specific, but at present signal/noise was not yet sufficient.

The meeting also noted that for dPCR, RNA also needs converting to DNA for detection by amplification, adding an additional transcription step. Dr Huggett recalled that early transcription processes had been extremely variable; the results for the CCQM-P199.b showed that considerable improvements had taken place. dPCR was also a good probe for variations in transcription efficiency, because of its high precision and its basis in counting.

Dr Mester noted that commercial standard manufacturers have released RNA standards within weeks of the start of the pandemic and asked how good those standards were. Dr Huggett replied that they provided a viable response for urgent need, but quantitation was inevitably poorer than the best that could be achieved and early detection capabilities based on these early materials may not be as reliable.

Dr Park said that the CCQM should be proud of the strong and practically useful response to the SARS-CoV-2 crisis. He also noted that this had relied heavily on the long experience of studies in GMO and other DNA quantitation applications, demonstrating the importance of CCQM's programme of fundamental studies.

7. ENSURING RELIABLE MEASUREMENTS FOR INFECTIOUS DISEASES: HOW WILL NMI AND CCQM ACTIVITIES EVOLVE?

A number of participants had been invited to give short presentations on their institute's plans in the infectious disease area following experiences in responding to the SARS-CoV-2 pandemic.

Dr R. Paroli (on behalf of NRC, Canada) said that NRC had to move very quickly to support testing of personal protective equipment, particularly N95 mask testing; NRC had very quickly repurposed their carbon particulate testing methods to support this. Overall, almost two thirds of NRC staff were involved in responding to SARS-CoV-2. In addition, they had worked hard to transfer capabilities to commercial partners to ensure sufficient testing volume. NRC had also assisted the rapid production of a SARS-CoV-2 spike protein RM to support antibody testing methods. For the future, Dr Paroli noted that the response required a broadly trained and adaptable workforce, able to transfer metrological principles quickly to very new areas. Long-term investments were also needed; Canada was investing $126m in a new NRC vaccine production facility.

Dr J. Braybrook (on behalf of LGC, UK) said that the drivers for emerging and re-emerging diseases were similar, including urbanization, globalization and other social changes. The NML at LGC considered that important considerations for accurate testing included the disease type; specimen collection ("pre-analytical" steps); extraction; aspects of the testing step itself (in particular including the different nature of targets for different assay methods); availability of commutable quantitative control materials; and the frequency of control determinations. The current pandemic had shown limitations such as the difficulty of providing accurate results in short turn-around times; needs for revalidation as new variants emerged; and a critical need for regular and rapid genotyping of emerging variants.

Dr Hongmei Li (NIM, China) explained that NIM were concerned with four measurement targets: the viral antigen; the viral genome; anti-virus antibodies; and vaccine components. Key issues were early detection; IVD product development and validation; routine quantitation; measurements supporting vaccine efficacy and safety; and post-intervention evaluation and screening. Dr Li identified a number of measurement problems. Early detection needed higher order RMs and a reference database; IVD development needed higher order reference measurement procedures and materials to provide reference values for validation; detection additionally needed routine QC materials; vaccine efficacy and safety needed additional RMs and measurements; and long-term response needed materials for Proficiency testing (EQA).

Dr D. Burke (NMIA, Australia) said that NMIA had quickly moved to prepare a reference material certified for viral genome count, using inactivated viral culture to provide coverage of the complete viral genome. The CRM included a set of concentrations for rapid calibration of qPCR. Each level in the series was measured individually by dPCR at NMIA. The values were corrected for transcription bias using IDMS measurements of synthetic RNA templates. The RM had been applied in an interlaboratory study of SARS-CoV-2 in wastewater to provide early warning of a need for increased

testing; the study returned results from routine testing laboratories the number of copies from below 1 mL^{-1} to c. 800 mL^{-1}, clearly indicating a need for further work to harmonize routine measurements. NMIA's future strategies included consideration of the likely need for inactivated virus CRMs; emphasis on improving quantitation; a need for comparisons for serological (protein) and genetic measurements; reference capabilities for vaccine production and extension of the new capabilities to other RNA viruses (such as HIV and hepatitis B and C).

Dr Young Bae (KRISS, Republic of Korea) summarized the KRISS strategy. This focused on three phases: diagnosis, prevention and treatment. KRISS activities for SARS-CoV-2 included exceptionally rapid preparation of reference materials (a three-month time scale). Dr Young Bae noted that SARS-CoV-2 had driven a rapid change in types of vaccine; several of the main SARS-CoV-2 vaccines were mRNA or DNA vaccines, some using synthetic RNA, instead of inactivated pathogen; KRISS believed these would provide a fruitful area of work for the CCQM Working Group on Nucleic Acid Analysis (CCQM-NAWG). Future plans for KRISS included a five-year project to develop capability for future pandemics. The new agenda included plans for strategic planning; fast-track development of RMs; quality control material production; and a focus on validation of emerging technologies for rapid pathogen detection.

Dr M. Tarlov (NIST, USA) described the NIST perspective for infectious disease measurements. The NIST response to SARS-CoV-2 had included rapid production of a research grade test material and a serology testing programme using flow cytometry methods, in collaboration with the LGC Seracare and the US National Institute of Health. NIST were also contributing to a WHO initiative to prepare WHO reference materials. Experience from SARS-CoV-2 at NIST highlighted a number of issues. He noted that greater innovation and development speed needed to be balanced with accuracy and robustness. NIST had had to adopt new ways of providing reference values, including provision of reference methods as well as RMs. NIST recognized a need to further strengthen competence in viral and microbial measurements, and consider measurement and characterization of more complex, clinically relevant, biological systems. Another effect of the pandemic was a marked increase in public awareness of the need for accurate measurement and testing.

In response to a question, Dr Li said that vaccine safety testing needed different measurement methods and RMs to the methods and materials used to support diagnostic testing.

Dr Huggett asked how CCQM can better align with other national/international organizations that are tasked with standardization of infectious disease testing. Dr Braybrook said that engagement with other key organizations in infectious disease testing and control was an important part of the CCQM strategy; Dr Paroli and Dr Park agreed.

Dr Wielgosz asked if the meeting felt that a CCQM workshop on infectious disease metrology and pandemic preparedness would be valuable. Dr Braybrook (LGC) said that this would help to ensure that CCQM could be more proactive than reactive in future emergencies. He also felt that a more detailed understanding of different strategies in different countries would be valuable; for example, the UK was not focusing strongly on antibody quantitation whereas others were. Dr Burke (NMIA) agreed. He also noted that it would be valuable to compare different measurement principles and said that a workshop to establish directions for future CCQM effort would be valuable. Dr Li (NIM) confirmed the need for CCQM members to share resources and knowledge on emerging technologies and felt that a workshop would help. Dr Paroli and Dr Tarlov also indicated support for a workshop. Dr Park drew attention to the "grand challenges" identified by CIPM and said that the focus on health made a workshop on the issue of infectious disease testing timely and relevant.

Further discussion of workshop arrangements was deferred to agenda item 17.3 (below).

8. CCQM 2021-2030 STRATEGY

Dr Park drew attention to the new CCQM strategy document (CCQM/21-18). He said that the strategy had been developed with thorough consultation of stakeholders, including a careful and detailed survey of needs. Dr Park introduced the proposed CCQM vision and mission statements and also listed seven strategic aims for CCQM. The vision and mission statements were:

- **The CCQM's vision**: A world in which all chemical and biological measurements are made at the required level of accuracy to meet the needs of society.
- **The mission of the CCQM is**: To advance global comparability of chemical and biological measurement standards and capabilities, enabling Member states and Associates to make measurements with confidence.

The strategic aims included: to contribute to the resolution of global challenges; to promote the uptake of metrologically traceable chemical and biological measurements; to progress the state of the art of chemical and biological measurement science; to improve efficiency and efficacy of the global system of comparisons for chemical and biological measurement standards conducted by the CCQM; to continue the evolution of CMCs to meet stakeholders needs; to support the development of capabilities at NMIs and DIs with emerging activities; and to maintain organizational vitality, regularly review and, if required, update the CCQM structure for it to be able to undertake its mission and best respond to the evolution of global measurement needs.

The draft strategy had been published for comment at the beginning of April, with a closing date of 7 May 2021 for comment. Detailed discussion of the document was deferred to item 12 (below).

9. CIPM STUDY ON EVOLVING NEEDS IN METROLOGY AND IMPACT FOR CCQM

Dr Park introduced the CIPM strategy study, "Evolving needs for metrology". The study identified five main challenges for metrology, together with two additional cross-cutting horizontal themes. The challenges included climate change and environment, health and life sciences, food safety, energy, and advanced manufacturing; the cross-cutting themes were digital transformation (including artificial intelligence and machine-readable information) and "new" metrology including, for example, intrinsic standards, sensor networks and distributed measurements.

CIPM actions in relation to these challenges included the establishment of interdisciplinary working groups covering broad themes; fostering close links with stakeholders; promotions of international comparisons and workshops; and deeper consultations with RMOs.

Dr Park observed that the CIPM strategy had clear implications for CCQM. The CCQM would need to embed relevant CIPM strategy elements into the CCQM programme, support CIPM expert working groups, further strengthen stakeholder links, promote inter-CC collaborations and to improve support from governments and other support networks.

10. REPORTS FROM THE CCQM WORKING GROUPS: 2021-2030 STRATEGY DOCUMENTS

10.1. CCQM WG 2021-2030 Strategy Elevator Pitch Presentations: OAWG

CCQM Working Group on Organic Analysis (CCQM-OAWG)

Dr L. Mackay (NMIA; OAWG Chair) summarized the OAWG ten-year strategy. A survey of member institutes had been undertaken to inform the strategy. The survey had covered both the types of service expected and the nature of comparisons that members felt necessary. The strategy also identified five priority sectors: Food; Clinical; Environment; Forensic and anti-doping; and manufactured materials and industrial products. The first three of these formed the main area of activity for core competency (track A) key comparisons over the next decade. In the food sector, food safety was the main priority, but nutritional content, packaging and processing contaminants and food authenticity were also recognized as important. In the clinical sector, provisional priorities had been established based on medical impact and harmonization status. Novel sampling methods and commutability of RMs were also identified as important to OAWG members and the community. In the environment sector, the WG felt that legacy contamination was a growing concern. The strategy also identified substances of particularly high concern, for example perfluorinated substances and endocrine disruptors. Microplastics were also an area requiring attention; Dr Mackay felt that this area would require a multidisciplinary approach and may need a workshop or similar event to establish priorities and appropriate working relationships.

The OAWG strategy included plans for core (track A) comparisons, which covered the three principal sectors. The strategy also provided for advanced metrology (improving purity, measurements for matrix materials and reference data). A second development stream covered instrumental methods with a focus on qNMR, high-resolution mass spectrometry and the development of compound-independent calibration using ICP-MS or related technologies. Stakeholder involvement would focus on organizations involved in laboratory medicine, ISO and its technical committees, and commercial/non-NMI CRM producers.

A full report of the working group activity (September 2020-March 2021) was also available (CCQM/21-06). During this period, the CCQM-OAWG had held four meetings via videoconference to finalize its strategy document and review proposed broad scope CMCs. Several key comparison reports, some with supplementary comparisons, had been finalized. The Final Report for CCQM-K146: Polyaromatic hydrocarbons in olive oil had been published in 2020 and the final report for a follow-on comparison, CCQM-K146.1 (on benzo[a]pyrene A in olive oil), had also recently been approved by CCQM WG chairs CCQM-K146.1 had used NIM, the co-ordinating laboratory, as the linking laboratory. Interestingly, results for the institutes participating in the follow-on KC were poorer than expected, apparently due to over-corrections for their deviations in CCQM-K146. The final report for CCQM-K148.a, on purity of bisphenol A expressed as a mass fraction, had been approved for publication in March 2021. The key comparison involved 17 institutes using both mass balance and qNMR techniques. The report provided a broad measurement claim, based on a mass fraction range and polarity rather than a single analyte and matrix, and would accordingly support broad CMC claims in future. Ongoing studies at draft B stage or earlier included CCQM-K133, on phthalate esters in polyvinyl chloride (PVC) as a model for low polarity analytes in plastics; CCQM-K156, covering the important global measurement issue of per- and polyfluoroalkyl substances in

groundwater; CCQM-K159 on mass fraction of leucine, phenylalanine in pooled frozen human plasma; and CCQM-K168, on trans-zearalenone in maize powder. Two solution/purity comparisons were planned for late 2021 and 2022: CCQM-K78.b, on methoxychlor and trifluralin as commonly occurring pesticides, and CCQM-K148.b, on the mass fraction of free base of oxytetracycline in a sample of oxytetracycline hydrochloride, with mass fraction of hydrochloride salt being an optional secondary measurand.

In discussion of the OAWG strategy, Dr Wielgosz asked which technical groups would need to be involved in CCQM work on microplastics. Dr Mackay said that there had been a number of international meetings in recent years which had identified a very broad range of measurement problems and parameters; she felt that this might require intervention at CIPM level to establish the right measurands and collaborations across Consultative Committees.

Dr Wielgosz reminded the CCQM that a workshop with accredited RM producers to see how best that community could be supported had been discussed within the SPWG. Dr Mackay agreed that this would be useful and perhaps could identify ways of allowing RM producers to benchmark their own capabilities against NMIs. Dr Park noted the restrictions on use of data by pilot study participants outside CIPM; Dr Mackay agreed and felt that RM producers would be better served by separate kinds of comparison, closer in nature to proficiency testing.

Dr Milton noted that the strategy included reference data that could become an “emergent measurement service” and asked whether this would raise new questions of ensuring comparability of data. Dr Mackay was sure that comparability was a key feature of reference data.

Dr Ellison asked how OAWG would see CCQM interacting with ISO, which was a large community with many, largely independent, technical committees (TCs). Dr Mackay said that some OAWG members felt that ISO activity on, for example, qNMR, was sometimes fragmented across TCs, and hoped to help bring these together. The OAWG strategy accordingly included a list of specific ISO TCs to work with to achieve this.

10.2. CCQM WG 2021-2030 Strategy Elevator Pitch Presentations: GAWG and IRWG

CCQM Working Group on Gas Analysis (CCQM-GAWG)

Dr Brewer (NPL; Chair, GAWG) summarized the GAWG strategy (CCQM/21-11). The strategy had used a member survey to establish the main priorities. The priorities included gas composition, isotope ratio, gas/liquid mixtures, particles and aerosols and development of new measurement technologies.

The strategy responded to needs in nine different sectors. Major themes across these included climate change and environmental measurement, health and life sciences and advanced manufacturing.

Strategic activities for the group focused on advancing the global measurement system. This included provision of isotope ratio RMs for greenhouse gases; implementation of regional greenhouse gas scales; supporting diversification of the energy gas supply via biomethane and hydrogen purity measurement; particle metrology for key new measurands, reactive gases; advanced spectroscopy and a stream developing new technologies.

To help deliver these, the GAWG had started a number of task groups, including (for example) one

on ozone cross-section. The strategy additionally included a prospective plan for key and supplementary comparisons.

Dr Brewer had provided a full activity report for year ending April 2021 in the form of a pre-recorded presentation. The group had met twice via videoconference during the year; as for many WGs, virtual meetings had shown appreciably higher attendance than in-person meetings. GAWG had recently published reports for BIPM.Q1-K1 (ozone), CCQM-K41.2017, measuring hydrogen sulfide in nitrogen, and four APMP supplementary comparisons on BTEX (benzene, toluene, ethylbenzene and xylene), methane in nitrogen, hazardous air pollutants in nitrogen, and carbon dioxide in nitrogen. The group additionally had four key comparisons and one associated pilot study at draft B (draft final report) stage, including CCQM-K150/P189 on particle charge and number, K117 on ammonia in air, K118 on natural gas composition, and K10.2018 on BTEX. Dr Brewer noted that CCQM-K150/P189 was the first CCQM comparison on particle charge and number, representing an important step towards physical characterization of airborne particles. CCQM-K10.2018, on BTEX at very low mole fractions, had shown good agreement for the considerable challenge but with some laboratories failing to agree within reported uncertainties. CCQM-K74.2018 compared preparations of nitrogen dioxide (NO_2) in nitrogen; the study had provided good information on both laboratories' gravimetric preparation and on the effect of the decay profile of nitrogen dioxide with time.

A further six key comparisons and three pilot studies were at draft A (preliminary report) stage or in progress; these covered a broad range of gases and other measurands, including N_2O in air, automotive gases, carbon and oxygen isotope ratios in CO_2, dimethylsulfide in nitrogen, SO_2 in air HCl in nitrogen, ambient CO_2 in air, oxygenated VOCs (volatile organic compounds) and purity of hydrogen gas.

The working group had also run the virtual workshop hosted by the BIPM on "Accurate Monitoring of Surface Ozone" in October 2020. The workshop discussed the implications of the revised Ozone Absorption Cross-Section published by a CCQM-GAWG task group in 2019 (see J T Hodges et al. *Metrologia* 2019, **56** 034001, DOI 10.1088/1681-7575/ab0bdd). This value is used in determination of surface ozone using UV spectrometry, and the BIPM.QM-K1 comparison, and the cross-section value consequently affects estimated atmospheric ozone concentrations. The revised value is approximately 1.2 % lower than the previous value, which would lead to increases in ozone amount fractions by the same relative value. This led to an agreement on implementation of the revised value for use in global monitoring, and the establishment of a new Task Group to oversee and plan global implementation of the new value.

The group also included work to support implementation of the revised ozone cross-section value; work on greenhouse gas scale comparisons; and development of advanced spectroscopic methods using invariant molecular or atomic spectroscopic properties. These activities were being carried out through separate task groups within GAWG.

CCQM Working Group on Isotope Ratios (CCQM-IRWG)

Dr Mester (NRC; Chair, IRWG) recalled that the WG was relatively new, having been formed in June 2018. He then summarized the steps taken to establish a strategy for the IRWG. As a new WG, much of the initial activity had been community building. The group had established three broad objectives: advancing science, improving comparability in isotope ratio measurements, and engaging stakeholders.

Dr Mester explained that isotope ratio measurements were important in many areas of science. For example, the redefinition of the SI units in 2019 required accurate measurement of isotopic composition for both the Avogadro project and for measurement of the Boltzmann constant, while the scale of fossil fuel use could be estimated from the atmospheric carbon isotope ratio. The principal technical areas important to the group therefore included climate measurement and improvement of the Commission on Isotopic Abundances and Atomic Weights (CIAAW) information on isotopic composition in the periodic table, a fundamental reference resource. Dr Mester also noted that isotope ratio measurements were subject to a traceability exception, often being expressed on delta scales.

Stakeholders currently included the forensic community via the Forensic Isotope Ratio Mass Spectrometry (FIRMS) network, the IUPAC Commission on Isotopic Abundances and Atomic Weights, standards groups such as CEN TC 460, working on food authenticity, and two EU project groups; SIRS, working on stable isotope reference standards, and STELLAR, working on isotope metrology to support climate action.

Comparisons of isotope ratio measurement capability had begun, with CCQM-K167/P211 on the 13C/12C isotope ratio in vanillin completed and CCQM-P204, on CO_2 isotope ratios, under way. CCQM-K167/P211 had been successful, showing good agreement for most participants.

In closing, Dr Mester said that the immediate goals for the group included refinement of the measurement space and the comparison programme; advancing discussion of the delta scale and its robustness as well as improving traceability to the SI; isotope reference data hosting and curation; and further development of inter-WG and inter-CC collaboration, particularly with CCQM GAWG and with CCRI for long-lived radionuclides.

Item 10.2: Questions and discussion

In discussion, Dr Brewer confirmed that the principal driver for the increased interest in particle metrology was air quality, though he noted that atmospheric particulates, and particularly particulate carbon, were also of interest as contributors to radiative forcing, which contributed to climate change.

Dr Wielgosz asked how the relationship between IRWG, CIAAW and IUPAC might be expected to develop with respect to the delta scale data that formed the basis of the Traceability Exception in this area. Dr Mester said that this was essentially a data curation activity and the metrological aspects had historically been managed by organizations such as IUPAC. He said that it was important that the scale in use should be within the reach of users, and he envisaged organizational linkages through arrangements such as the recently signed IUPAC-BIPM memorandum of understanding. This might include joint work on delta scale definitions.

Dr Milton noted that the IRWG was addressing some key issues for some of the other CCQM WGs and asked how members would manage activity across in the IRWG and also IAWG or GAWG. Dr Mester said that IRWG studies will be conducted in close collaboration with the other CCQM working groups, as necessary.

10.3. CCQM WG 2021-2030 Strategy Elevator Pitch Presentations: IAWG, EAWG, SAWG

[CCQM/21-13,15,16,19,22,27]

CCQM Working Group on Inorganic Analysis (CCQM-IAWG)

Dr M. Winchester (NIST; IAWG Chair) presented the IAWG strategy. He recalled the effect of the SARS-CoV-2 pandemic on the WG's activity; the result was a backlog of studies. He also noted that like other WGs, online meetings had led to much higher attendance than in-person meetings; as a result, he was considering a hybrid meeting programme for the future.

In addition to the general aims of supporting SI traceability, supporting CMCs and promoting broad scope CMC claims, the IAWG strategy identified four growth areas, including nanoparticle metrology; element-based measurements of biomolecules; elemental speciation measurements and direct measurements of soils (including imaging). Technically, the group also saw a particular need for development of measurement methods for non-metallic elements.

The group had developed a framework for broader CMC claims, allowing coverage of a wider range of CMCs with a realistic number of key comparisons. He also noted that IAWG had experimented with a new decision tree for deciding on the approach for KCRV estimation for consensus KCRVs.

Dr Winchester noted that particle counting was a new area for the group, following from the emergence of techniques such as single particle ICP-MS. This built on existing experience on ICP technologies but required extensive collaboration with other groups.

In addition to the verbal report on IAWG strategy, a full written report on IAWG activity had been made available in advance of the meeting. The IAWG had published one pilot study and three key comparison reports in the year to April 2021: CCQM-K34.2016.1 (joint with EAWG) on assay of high purity potassium hydrogen phthalate (KHP), an important buffer salt; CCQM-P160, on isotope ratios and molar mass measurements of silicon isotopes in isotopically enriched silicon; CCQM-K143/P181, comparing preparation of copper calibration solutions; and CCQM-K152, comparing capabilities for assay and purity of potassium iodate, with the accompanying pilot study report (CCQM-P192) in preparation. Measurements for a further three studies had been completed, including CCQM-K144/P182 on trace elements in alumina powder, CCQM-P194 on particle number concentration of gold nanoparticles in colloidal suspension, and CCQM-K151/P191, run jointly with the PAWG and (for IAWG participants) using sulfur-based ID-ICP-MS to determine mass fraction of a recombinant protein in an aqueous calibration solution. Measurements were under way for studies on elements in seawater (CCQM-K155/P196) and platinum group elements in automotive catalysts (CCQM-K161/P203), and a further seven studies were at registration or planning stages.

CCQM Working Group on Electrochemical Analysis (CCQM-EAWG)

Dr S. Seitz (PTB; Chair, EAWG) summarized the strategy. He reviewed recent studies; eight key and supplementary studies had been coordinated since 2016. The present work plan included a range of pH, coulometry, and conductivity studies. A small number had been deferred due to the SARS-CoV-2 outbreak.

Turning to the strategy he noted that electrochemical sensors were reducing in cost and increasingly widely used; there was a clear need to underpin these in future. Specific technical areas to be addressed included ocean observation (including salinity, pH, O_2 and others); the extension of measurement ranges over wider temperature and pressure ranges and into different matrices;

specialist coulometric comparisons for new analytes, measurements for lithium-ion batteries, and work to improve traceability for electrochemical sensors downscaled to micro- and nano-scale. A task group was being formed to examine problems in Li-ion batteries, which was a new area of work for EAWG, and terms of reference would be produced.

In common with other WGs, the group expected to work on broadening CMCs and reducing the number of comparisons, better ways of supporting CMCs related to CRMs, and new approaches related to traceability for the large and diverse communities using electrochemical measurements and sensors.

Dr Seitz had additionally provided a full activity report for the year ending April 2021 in the form of a pre-recorded presentation. The group had met twice, online, during 2020 and met again in the week preceding the 2021 CCQM plenary. To date, EAWG had organized 32 key comparisons and 20 pilot studies, supporting 57 CMCs for electrolytic conductivity, 114 for pH and a small number in other categories. The working group had completed five key comparisons over the preceding year, most in cooperation with IAWG (above). CCQM-K152 (joint with IAWG) comparing assay and purity of potassium iodate; CCQM-K34.2016 on assay of high purity potassium hydrogen phthalate; CCQM-K73 on concentration of H^+ in HCl solution; EURAMET.QM-S12, jointly with other EAWG members, included ten participants and measured water conductivity; APMP.QM-K18.2016 on pH of carbonate buffer solution, again run jointly with members of EAWG. A further comparison, CCQM-K19.2018, on pH of borate buffer solution, was in progress. EAWG were also planning a study on seawater pH, which was expected to take place in mid-2022.

Further details were given for CCQM-K152 and EURAMET.QM-S12. CCQM-K152/P192 had allowed participants to demonstrate capability for measurement of non-metallic elements in high purity salts as well as to perform coulometric or titrimetric assay. EURAMET.QM-S12 was important because the study had successfully extended the conductivity measurement range to pure and ultrapure water, which was particularly important for the semiconductor industry. The study had included conductivities at four levels, from 0.05 $\mu S\ cm^{-1}$ to 50 $\mu S\ cm^{-1}$.

Dr Seitz additionally noted that EAWG had revised its own guidance document for CMC claims, which provided additional detail for electrochemical CMCs. The revised document was publicly available on the BIPM website.

CCQM Working Group on Surface Analysis (CCQM-SAWG)

Dr T. Fujimoto (NMIJ/AIST; Chair, SAWG) provided a summary of the SAWG strategy. He said that surface analysis was a horizontal field that had impact in almost all areas of science and engineering. The strategy accordingly needed to cover a very wide range of sectors, including all those identified in the CIPM strategy (climate, health, food safety, energy and advanced manufacturing). Dr Fujimoto recalled the four main strands of the SAWG strategy: to carry out key comparisons underpinning capabilities for spatially resolved chemical surface analysis at micro- and nanoscale; to underpin the development of reference measurement systems in spatially resolved chemical surface analysis at the micro and nanoscale; to act as a forum for the exchange of information about the research and measurement service delivery programmes; and to provide a scientific basis for the measurement comparability that other WGs are seeking to establish. The strategy also identified a number of key stakeholders, who the SAWG expected to work with through its members. These included NMIs and DIs, metrology organizations including regional metrology organizations, a wide range of industry sectors, national and international trade organizations, professional bodies, and standards development organizations (SDOs). The main route to engaging with stakeholders would be through SDO activities, many led by SAWG members, ISO TC229

(nanotechnologies) and ISO TC201 (surface chemical analysis) were considered particularly relevant.

Dr Fujimoto explained that the SAWG work plan was aligned with particular technical challenges in surface analysis. Outer surface analysis focused on measurements of surface composition and thickness of the surface layer. Over the ten-year period of the strategy, SAWG foresaw new studies of graphene surfaces from approximately 2025 onwards. From 2022 onwards the group intended to add studies of deeper layers, measuring amount of substance and moving from pilot studies to key comparisons. The group also had a strong interest in adsorption isotherm classification, for which the specific surface area based on BET theory was a well-established and internationally accepted measurand. The group intended to ensure that its key comparisons on surface area measurement would cover the complete measurement space to ensure support for current and future NMI and DI measurement services and associated CMCs.

Other planned areas of work included number concentration of particles, surface composition of ionic liquids, the development of traceable quantitative methods using Raman microscopy and, from the middle of the period covered by the strategy, pilot studies for imaging, multimodal measurements and amount of substance in drug delivery vehicles, all supporting diagnostic and therapeutic device development and manufacture.

A written report on SAWG activity for the year was also available for the meeting. In addition to development of the strategy document, one pilot study, CCQM-P190, had been completed and two new key comparisons had been started. The aim of CCQM-P190 had been to demonstrate equivalence in the measurement capability of national metrology institutes for the thickness measurement of hafnium (IV) oxide (HfO_2) films. HfO_2 is an emerging alternative to SiO_2 in semiconductor applications. The report had been finalized in 2020 and was available on the BIPM website.

The two new SAWG key comparisons were CCQM-K157 and CCQM-K172. CCQM-K157 was a further comparison on HfO_2 film thickness; layer density and mass deposition were additional, optional, measurands. CCQM-K172 will compare measurements of specific adsorption of argon on zeolite at liquid argon temperature. The study is intended to demonstrate the comparability of measurement protocols at NMIs and DIs for addressing the porosity properties of technologically important microporous solids.

Item 10.3: Questions and Discussion

In discussion, Dr Wielgosz asked whether the decision tree in use by IAWG for KCRV calculation was the same as that in use by the OAWG. Dr Winchester confirmed they differed in the level of detail and in some decision points.

In response to a question, Dr Fujimoto said that operationally defined measurands such as specific surface area could be SI-traceable. He noted that CCQM had formed a task group on this issue and a policy on operationally defined measurands had been agreed. Dr Fujimoto confirmed that SAWG activities and comparisons were fully consistent with the established policy and that the group was working to ensure the highest possible metrological standards in surface area measurement.

10.4. CCQM WG 2021-2030 Strategy Elevator Pitch Presentations: PAWG, NAWG, CAWG

CCQM Working Group on Protein Analysis (CCQM-PAWG)

Dr J. Melanson (NRC; Chair, PAWG) presented the PAWG strategy. He thanked the vice-chair, Dr Swart, for undertaking a member survey that helped to inform the strategy. This had identified the main stakeholders (which included other NMIs) and the principal services provided. The main stakeholder groups were NMIs, PT providers, clinicians, and the IVD industry. The most common services were RM certification and provision of reference measurements.

Purity studies in PAWG were planned by reference to relative molecular mass modulated by extent of crosslinking and modification. Studies so far had focused on comparatively simple peptides, with larger proteins originally to be considered from 2027 onward. The need to respond to the SARS-CoV-2 emergency had, however, obliged the group to conduct an early study on a SARS-CoV-2 antibody, a much larger and more complex protein. Moving to studies in more complex matrices, Dr Melanson explained that matrix studies were planned to cover a space described by molecular mass and mass fraction of target analyte, moving from higher to lower mass fraction of protein or peptide over time. He additionally thanked PTB for leading recent studies on complex matrices.

The PAWG strategy also included plans for broader scope claims, including criteria for such claims. At present, PAWG felt that only capabilities for purity of simpler peptides had been demonstrated sufficiently to permit broad CMC claims.

A further report on PAWG activity over the previous year had been provided in the form of a video presentation, given jointly by the PAWG Chair and Vice-Chair. This included further detail on the development of the PAWG strategy, which had taken account of several workshops on SARS-CoV-2 testing, protein analysis in food, in cells (jointly with CAWG) and on SI traceability of protein measurements in tissues. A study of important peptide and protein measurements requiring SI traceability had also been undertaken, taking account of national regulations as well as stakeholders' reported priorities. To cover the required range of measurement problems, PAWG had formed a number of focus groups.

Two studies were currently ongoing, including the study on SARS-CoV-2; the second was on haemoglobin and glycated haemoglobin, which was important for diabetes treatment. A key comparison, on parathyroid hormone (PTH) was planned for 2022-2023; additional purity studies on cyclosporin A, vancomycin, procalcitonin, apolipoproteins and on microtubule-associated phosphoprotein (τ-protein) were planned to cover different challenges. Dr Melanson thanked BIPM for coordination of many of the working group's purity studies to date. Further studies were planned to cover proteins and peptides in biological samples such as blood or serum. Finally, a small number of studies were planned to underpin CMCs for measurement of enzyme activity using IFCC methods.

The results for CCQM-P201, on total haemoglobin in whole blood, were presented. Five NMIs participated, though most used more than one measurement method to test capability. The results appeared to show consistent differences between different measurement methods, with evidence that the dispersion of results was not fully explained by the reported uncertainties. Further study suggested that some separative methods were failing to detect haemoglobin bound to haptoglobin, leading to approximately 2 % underestimation of total haemoglobin. This work had helped to inform

planning for a proposed key comparison on SI-traceable measurement of total haemoglobin. The key comparison would take advantage of a RELA (external quality assessment for Reference laboratories) study in late 2022.

Updates on two purity studies were also reported on the hexapeptide HbA0 (also known as VHLTPE) (CCQM-K115.2018/P55.2. 2018), and on the glycated form, glcVHLTPE (CCQM-K115.c/P55.2.c). Additional unexpected peptide impurities had been detected in the comparison material, which had made the comparison more challenging than initially anticipated. The comparisons were run in parallel and would support reference systems for diabetes diagnosis and monitoring.

Dr Melanson gave a summary of the results of CCQM-P216, on quantification of SARS-CoV-2 monoclonal antibody in solution. This was a capacity building study, focused on amino acid and peptide quantitation after digestion. The study had been accomplished in approximately six months. Results were more variable than simple peptide studies but nonetheless showed encouraging agreement. The study will be followed up by further work on intact antibodies.

CCQM Working Group on Nucleic Acid Analysis (CCQM-NAWG)

Dr Huggett (LGC; NAWG chair) provided an overview of the NAWG strategy (CCQM/21-17). This had, like others, been developed with support of a member survey. The survey had shown that most current CMCs held by members were related to food applications, especially GMO determination, with one related to human genetics. Members foresaw a need for a broader range of capabilities in the medium term, particularly for medical applications and biotechnology.

Dr Huggett explained that the ‘measurement space’ for the nucleic acid WG could be broadly described in terms of the type of measurement, the number of particular sequences of interest (‘target sequence’) and the complexity of the matrix. The challenge increased on moving from detection of a nucleic acid target, through relative quantitation (such as proportion of genetically modified material), to absolute quantitation, such as the number of copies of a particular target. Similarly, moving from one known target sequence to quantitation of several well-known targets and then to ‘non-targeted’ quantitation, and from simple to complex matrices, each provided greater measurement challenges. Most past NAWG studies had involved relative quantitation of known targets in relatively complex matrices; a small number of recent pilot studies had explored absolute quantitation.

The strategy included a nine-year programme of comparisons. In the food area, comparisons were planned to cover the traditional AOAC ‘food triangle’, describing matrix composition in terms of fat, protein and carbohydrate; the measurement was typically a relative quantitation for detecting adulteration. Dr Huggett noted that food matrices could sometimes be sufficiently similar to human tissue to underpin capabilities for medical applications, particularly in demonstrating effective extraction. To support medical applications, the study programme included studies on species identification, DNA methylation (important for gene regulation), and bacterial and viral pathogens. Later studies were expected to further improve SI traceability for nucleic acid quantitation in matrix materials, develop capabilities for characterization (such as purity for reference standards), and to underpin broad scope CMC claims. Studies exploring ‘non-targeted’ nucleic acid measurement were foreseen towards the end of the study programme.

A written activity report had also been made available. Ongoing studies included key comparisons on relative quantitation in a high protein matrix (CCQM-K86.d) and on HER2 copy number in human tissue (CCQM-K176); HER2 is an important gene for breast cancer treatment. Ongoing and

completed pilot studies included CCQM-P184, determining copy number concentration and fractional abundance of mutated target sequences mixed with wild-type DNA, and CCQM-P199, measuring HIV-1 RNA copy number quantification. For CCQM-P199, a high-level material had been quantified by IDMS; comparison with digital PCR (dPCR) results had identified a proportion of large molecule impurities, inflating the IDMS value. Further follow-up work had also evaluated comparability between one- and two-step reverse transcription dPCR (RT-dPCR) and the chemical measurement methods used to determine a reference value; this work had been useful in establishing uncertainties in RT-dPCR, a key measurement method for RNA, including RNA in viruses. A particular success for NAWG during the year had been the completion of CCQM-P199.b, on SARS-CoV-2 RNA, discussed separately above (item 6).

Dr Huggett also acknowledged the many NAWG members who had led studies during the year and who had assisted in preparing the NAWG strategy, including staff at NIST, KRISS, NIB, VNIIM, NPL and LGC.

CCQM Working Group on Cell Analysis (CCQM-CAWG)

Dr Campbell (LGC; CAWG chair) began with thanks to staff at NIM, NIBSC, NPL, INRIM, NMIJ, VNIIM, LGC and NIST for their help in developing the CAWG strategy. He then provided a brief report, including comments on the CAWG strategy (CCQM/21-09), to the meeting.

Cell measurements covered a wide range, as microorganisms were important in food and water, environmental monitoring, diagnostics, drug discovery and in advanced therapies. The CAWG strategy had been developed with the help of a member needs survey; the survey showed a wide range of different technologies and Dr Campbell noted that the group was still working to identify any that could properly serve as reference methods; in part this was because of the number of sources of uncertainty for many common techniques. He felt that initial key comparisons on enumeration would need to concentrate on label-free counting systems due to the comparatively small number of uncertainty sources; dye-based systems, expression systems and probe binding systems each added sources of uncertainty despite their advantages in routine measurement.

The group was currently working via pilot studies; one was complete; one in progress and a range were proposed for future years. These were driven by the need to develop a sound metrology framework for cell measurements, including approaches for measurement uncertainty. Studies had commenced with cell counting problems; these were being developed towards increasingly complex problems that included, for example, increasing levels of sample manipulation and the identification of cells with particular bioactivity as well as simple enumeration.

The CAWG had constructed a ‘roadmap’ of objectives and corresponding activities for the next decade. The principal measurand was cell count or concentration; the main themes were support for reference material development, and support for identification and classification. The aim was to develop measurement capabilities for cell enumeration in suspension, and to build on that to address enumeration of cells adhering to surfaces and, later, enumeration for viability and cell function. Initial steps were able to build on established approaches; for example, enumeration of cells in suspension relied on established methods for traceable volume measurements or, alternatively, density and mass measurement in a flow system, and there were established systems for checking and calibrating flow cytometry equipment using fluorescent bead suspension.

Dr Campbell listed a number of priorities for the CAWG. These included

- Establishing reference methodology for cell counting

- Effective collaboration with other CCQM WGs and alignment with CCQM challenges
- Continued liaison with JCTLM and relevant ISO committees
- Establishing CAWG task groups for specific challenges, including metrology for cell viability and particular bioactivities
- Exploration of new areas for cell measurement, such as biofilm measurements for solar panels and measurements of algal cultures for CO_2 conversion
- Arrangement of workshops to help inform further work.

A written report on CAWG activity for the year had also been made available. In addition to the work done to establish the future strategy, the report summarized progress on CAWG studies over the previous year. CCQM-P123, on number and geometric properties of cells adhered to a solid substrate, was complete, with a final study report agreed in November 2020. Nine participants had demonstrated a good level of agreement in the quantification of cell number per area (cell density), area occupied by cells (cell confluency) and average cell area on a planar surface. CCQM-P217, on enumeration of fixed peripheral blood mononuclear cells in suspension (led by NIBSC in the UK) was currently in progress. The study aimed to examine participant ability to evaluate cell counting measurements using a dilution series, and to improve understanding of uncertainties in generating a dilution series for cell suspensions. The study involved ten participants; results were expected in mid-2021.

Four pilot studies were at the planning stage. CCQM-P197, intended to measure proliferative stem cell number per unit area (led by NPL, UK) will expand on the complexity introduced in CCQM-P123 by requiring enumeration of dividing cells. CCQM-P205, on enumeration of membrane intact E. Coli (led by NIM China) will support the development of higher order methods for the enumeration of membrane intact E. Coli in drinking water, an important measurand for drinking water safety. Two further pilot studies, yet to be registered, are planned to cover enumeration of CD4 and CD8 lymphocytes expressing interferon gamma, and particle number concentration measurements. The first of these would form a test of capabilities for enumeration of cells with particular bioactivity; the second, in conjunction with IAWG and still under consideration, would be important for establishing SI traceability for future cell concentration measurement.

Item 10.4: Questions and Discussion

Dr Wielgosz asked which international organizations with interests in biological measurement could be approached to form liaisons with CCQM to enhance the impact of activities in PAWG, NAWG and CAWG. A number of suggestions were made. The meeting noted that CIPM already had a memorandum of understanding with WHO and the IFCC, and that the “bio” WGs already had links with some laboratories active in WHO programmes, particularly NIBSC, which developed and distributed WHO reference materials. NAWG members also had links with the International Working Group on the Standardisation of Genomic Amplification Techniques (SoGAT). There were also specialized organizations in the cells area, such as the International Society for Cell and Gene Therapy, the Foundation for Accreditation of Cell and Gene Therapy, and the International Council for Standardization in Haematology (ICSH). ICSH had recently become a JCTLM Executive Committee Member Organization.

10.5. BIPM Programme on Metrology in Chemistry [CCQM/21-42]

Dr Wielgosz (BIPM) presented a summary of the BIPM programme on Metrology in Chemistry, with a full pre-recorded presentation having previously been made available as CCQM/21-23. The BIPM Chemistry Department supported the CCQM mission by providing coordination of comparisons; international liaison and coordination activities; and capacity building and knowledge transfer projects including a strong visiting scientist programme.

Visiting scientists were an important part of the department's programme, both to bring expertise into the department and to develop scientists from other institutes. Approximately 50 scientists from 23 countries had visited the BIPM Chemistry Department in the previous five years, and in the last year, due to the pandemic, this had been replaced by a programme of virtual secondments and on-line knowledge transfer projects, with the first of these attracting almost 100 participants from NMIs and DIs, and which would be run over a 6-month period.

The BIPM laboratories support the CCQM programme of comparisons by coordinating comparisons for the GAWG, OAWG, IRWG and PAWG. Examples included comparisons of CO_2 in air standards such as BIPM.QM-K2 and BIPM.QM-K5, and CCQM-P204 for isotope ratios in CO_2, supporting monitoring and emissions authentication. The department also coordinated the OAWG purity and peptide comparisons run by PAWG. This included support for CCQM-P216 study, on SARS-CoV-2 antibody quantitation. He demonstrated how the BIPM activities contributed to the overall resources available for CCQM comparison co-ordination, using the graph from the CCQM GAWG strategy document, which summarized the number of laboratories that had coordinated CCQM comparisons. Whilst the GAWG had more than 30 member institutes, the vast majority of comparisons were coordinated by only five laboratories of which the BIPM was one. The GAWG strategy foresaw more NMIs developing capabilities and knowledge to allow them to coordinate comparisons, and the BIPM department would be setting up a twinning and mentoring programme for NMIs new to CCQM comparison coordination.

The department was additionally supporting the two new CCQM GAWG task groups one on ozone cross section global change management and the second on greenhouse gas (GHG) scales. The latter would be supported by reference and comparison facilities at the BIPM and would lead to the development of a machine-readable database for relationships between different CO_2 in air gas scales and standards. The department also provided reference data in collaboration with a number of NMIs for a heptad of internal standards used for qNMR, a methodology developed in conjunction with the CCQM OAWG.

Dr Wielgosz also reported that the department's knowledge transfer activities included programmes on metrology for safe food, for clean air, and for laboratory medicine. The programmes were proving successful and had enabled a number of new services from participating NMIs, providing the example of mycotoxins standards in support of food safety and analysis. He noted that some of these were moving to online programmes, particularly a forthcoming course on metrology for safe food and feed. Based on subscriptions, this was also proving a popular way of disseminating information. He additionally drew attention to BIPM's new e-learning platform, launched on 26 April (see https://e-learning.bipm.org/).

The group's coordination and liaison activities included the CCQM executive secretary role, including support for the new task groups emerging within CCQM WGs, interaction with other

international organizations, as well as support for the JCTLM database and support for CCQM and CIPM workshops. Dr Wielgosz closed with a reminder that BIPM would be running one such workshop, on Metrology for Climate Action, in 2022. In response to a question, he confirmed it was intended to also cover oceanic measurements; the workshop was not limited to atmospheric measurements.

Item 10.5 Questions and discussion

The meeting congratulated the BIPM Chemistry Department on their strong support for CCQM and welcomed the launch of the e-learning platform.

11. AD HOC CCQM WG ON UPDATE OF KCRV ESTIMATION GUIDANCE

Dr Ellison explained the reasons for proposing the establishment of a new *ad hoc* working group and the CCQM Strategic Planning Working Group (CCQM-SPWG) decisions taken to date.

CCQM had approved a guidance document, CCQM/13-22 ("Estimation of a consensus KCRV and associated Degrees of Equivalence"), for reference in 2013. The document had been prepared by a CCQM *ad hoc* working group chaired by Prof. Maurice Cox at NPL and included members from most CCQM WGs as well as additional experts. The document was available on the CCQM website for working groups to use at their discretion. The document gave general guidance on the process of reviewing key comparison results, selecting a calculation method for the key comparison reference value, and calculating degrees of equivalence given a particular KCRV calculation approach. An Annex gave a collection of the calculation methods.

Since release of the document, use over time had identified a small number of editorial corrections. More importantly, a further decade of CCQM work on pilot and key comparisons had generated new experience, and new and useful statistical methods and software had emerged to support KCRV estimation.

These factors had been drawn to the attention of the CCQM SPWG in early 2020. SPWG had agreed that it was timely to propose an update of CCQM/13-22 and had initiated a small drafting group, convened by Dr Ellison, to prepare draft Terms of Reference for an *ad hoc* WG to undertake a revision. The drafting group had provided an initial draft of the terms of reference for SPWG consideration and, after taking account of comments, SPWG approved draft terms of reference for circulation to all CCQM members as a basis for establishing an *ad hoc* working group. The proposed terms of reference were given in CCQM/26-08. CCQM was accordingly invited to consider the terms of reference and approve the formation of an *ad hoc* Working Group for Revision of CCQM KCRV Guidance, and to appoint a convenor for the *ad hoc* working group.

Dr Wielgosz said that this should be considered an SPWG recommendation to CCQM, and he proposed that Dr Ellison convene the group as a formal Task Group of the CCQM.

Dr Mester asked how members would be appointed. Dr Ellison drew attention to the proposed terms of reference, which provided for members to be appointed by CCQM WGs. On formation, the task group would be expected to invite members from the CCQM WGs together with additional experts subject to permission from the CCQM President. In response to a suggestion, Dr Ellison agreed that it would be helpful if the WGs would consider nominating members who had contributed to the

development of individual WG practices for comparison data handling.

The President asked what the expected time scale for revision would be. Dr Ellison said that since this was currently expected to be a modest revision, he hoped the group would be able to provide an initial draft for the 2022 meeting of the CCQM and that completion in two years should then be possible.

The meeting agreed to form the task group and appointed Dr Ellison as the convenor.

Items 10 – 11: General questions and discussion

The President invited general questions on topics presented during the day or in written reports.

In discussion, Dr Botha noted that many WGs were evolving individual guidance and policies on (for example) handling of data, participation and structure of the WGs, and detailed study procedures. She asked how WGs were collaborating to harmonize these documents. Dr Wielgosz said that there were indeed some differences in detailed procedure. He noted that the KCWG were planning to form a task group on the question of sub-optimal performance in KCs and guidance on subsequent CMC claims, addressing some of these questions. He further suggested that harmonization of procedures across WGs was primarily an issue for the CCQM-SPWG.

The President asked Dr Botha to prepare a short list of issues for harmonization, for the attention of the SPWG.

Dr Huggett noted that interaction with the WHO was an issue for all of the biological WGs and asked how that could best be addressed. Dr Wielgosz replied that the proposal, in the CCQM strategy document, to form a horizontal task group on stakeholder engagement would provide a good forum to address this (see item 12 and decision 4, below).

12. OVERVIEW AND STATUS OF CCQM STRATEGY DOCUMENT 2021-2030

Dr Park opened the third day of the meeting with an overview of the draft 2021-2030 CCQM Strategy Document. The document had been developed starting with the CCQM vision and mission statements and strategic aims and reference to the CIPM study on evolving needs for metrology. It had then been extended using inputs from individual working groups and stakeholders. The draft had been published for comment, with a closing date of 7 May. Dr Park noted that this was an important document for CCQM and encouraged members to provide any final comments.

The document identified scientific, economic, and social challenges across nine major sectors, provided a vision for CCQM, as well as activities to support the strategy including 33 specific actions to progress measurement science in the field. The activities included the promotion of the fundamental science of metrology, improving stakeholder engagement, promoting global comparability, and strengthening interaction with regional metrology organizations. Dr Park felt that many of the challenges would require interdisciplinary collaboration and hoped to encourage wider discussions on how best to achieve this in the future.

To promote global comparability, CCQM aimed to move towards broad scope CMC claims. To date, there had been only a slight decrease in number of chemistry and biology CMCs (6193 from 6632 in 2019); this appeared to reflect different approaches in different NMIs, some of whom still needed to

develop closely defined capabilities for national needs, whereas others were beginning to use broad scope CMCs to underpin a wide range of related services.

The strategy provided for four general actions to promote effective action with RMOs, including maintenance of the existing strong interaction between CCQM and relevant RMO technical committees, continued coordination of linked and supplementary comparisons, an increased focus on capacity building and technology transfer and initiation of a mentoring programme for NMIs coordinating comparisons for the first time.

Dr Park additionally noted the importance of continuing support from the BIPM Chemistry Department in order to progress the CCQM strategy.

The strategy identified stakeholder engagement as a key tool in promoting the activities and impact of the CCQM and provided for a more structured approach to promote stakeholder engagement. To carry this forward, the strategy proposed the establishment of a new CCQM Task Group to develop mid- and long-term plans for stakeholder engagement, including:

- Extension of the CCQM Liaison membership to represent the expanded technical coverage
- Interaction with other Consultative Committees
- Strong participation in sector-specific fora established by the CIPM
- Further use of Task Groups to deliver the CCQM mission.

Dr Park proposed that Dr Richard Brown (NPL, UK) be appointed as convenor of the Task Group.

In respect of membership, Dr Wielgosz (BIPM), Dr P. Fisicaro (LNE), Dr Z. Mester (NRC), Dr J. Huggett (LGC) and Dr Botha (NMISA) offered to participate. Dr Guettler said that PTB would contribute, with himself as the contact in the first instance. Dr Braybrook offered to seek a further participant within LGC. Dr Brown additionally proposed that CCQM WGs be invited to propose members of the group.

The meeting **agreed** to form the task group with immediate effect and to appoint Dr Brown as convenor.

Questions and discussion on CCQM Strategy Document 2021-2030

Dr Park invited further discussion of the Strategy.

Dr Botha noted that the list of individual activities included several actions which might be expected to involve more than one working group, and asked what arrangements were in place to promote effective collaboration and avoid unnecessary duplication of effort. Dr Wielgosz explained that this would normally be considered in formulating working group plans, with the SPWG available to identify opportunities for coordination.

There were no further comments during the meeting, but Dr Wielgosz reminded members of the closing date for comment (7 May 2021) and looked forward to receiving any further comments by correspondence.

13. KEY COMPARISON AND CMC QUALITY WG REPORT

Dr Sin presented a report on the work of the CCQM WG on Key Comparisons and CMC Quality (CCQM-KCWG). The WG had met twice during the year and had considered a total of 403 CMCs. These came from almost all RMOs, though GULMET had not submitted CMC claims in the past year. The majority of submitted claims (359) required modifications before acceptance.

As of April 2021, there were 6193 chemical and biological measurement CMCs on the database. This was a reduction from the previous year, and the lowest value since 2016. The reduction probably reflected voluntary withdrawal of some CMCs in recent years, together with the growing use of broad scope CMC claims. The three most frequent measurement categories among CCQM CMCs were gases (2362), food (771) and pure chemicals (648). Of the approximately 400 new and revised CMCs reviewed in the year, 91 had been for new food-related CMCs, while 48 had been for revisions to gas CMCs. Biological materials, organic solutions and gases had also seen notable numbers of new claims. Reviewing claims by CCQM working group technical area, OAWG, IAWG and GAWG accounted for nearly 90 % of new and revised CMC claims. APMP and EURAMET were the two most active RMOs.

Reporting on progress with claims, Dr Sin said that approximately 80 had already been approved and published; this was more than usual for the present point in the annual cycle.

Dr Sin presented a list of KCWG members, and was pleased to note that, as well as strong representation from all of the RMOs involved, every CCQM WG had a representative attending on-line meetings for the present cycle.

The ‘core capability’ and broad scope concepts were being applied by several working groups. For CMC review, this meant fewer claims, but claims required more expert appraisal to judge whether a particular CMC was supported by the studies and core capabilities cited in support.

This had been the first year in which the new KCDB 2.0 had been used for CMC submission and review. This had posed several challenges. Preparatory work had been carried out in parallel with ongoing CMC review, increasing the workload. Despite the extensive preparatory work, the submitters and the WG were still learning how best to use the system. The change in the process required adjustments for both the WG and stakeholders, and some roles and responsibilities had changed. As a result, the “Frequently Asked Questions” section had already been updated with some common questions.

Noting the additional work needed to apply the new KCDB process, regular review had been suspended for one year. Approximately 1500 existing CMC claims were, however, over ten years old and had not been reviewed; these would accordingly be given priority when regular review recommenced.

In closing, Dr Sin thanked all of the KCWG members and reviewers, and the BIPM staff supporting the KCWG, particularly Dr Picard and Dr Maniguet.

13.1. Questions on KCDB 2.0 CMC review implementation

In discussion, Dr Winchester asked for the KCWG’s views on the applicability of the principle of ‘broad scope’ CMCs. Dr Sin said that this principle was not yet harmonized and the KCWG had

recently decided to form a task group to formulate recommendations on the use of broad scope claims to improve harmonization. Dr Milton noted that the CCQM had historically led on the process of CMC review and that, as a result, the new system had been modelled closely on the CCQM authorities and process. He hoped that this would mean that the general process would be reasonably familiar and that the software would handle routine tasks automatically. Dr Sin felt that once users became familiar with the system, it would provide real efficiency gains.

Dr Park asked whether the group had seen different approaches or other problems in relation to broad scope claims. Dr Sin said that nearly all CCQM WGs had developed their own strategies to accommodate broad scope claims. This presented new challenges for the KCWG, hence the decision to provide recommendations for harmonization.

13.2. Presentation and approval of planned CCQM comparison list

Dr Wielgosz presented the circulated list of planned CCQM comparisons requiring approval.

The OAWG proposed a track A (core) key comparison on a polar analyte in high protein food. The study was included in the 2021-2030 OAWG strategy and was a priority area for the food sector. The study is provisionally planned for 2022. The coordinator had yet to be determined.

The GAWG proposed a track A/C key comparison, provisionally designated BIPM.QM-K2, on-going comparison for carbon dioxide in air. The comparison was considered essential to enable NMIs and DIs to demonstrate measurement capabilities and address requirements for atmospheric monitoring of CO_2. The coordinator would be BIPM. A pilot study was additionally proposed to prepare for BIPM.QM-K2.

The EAWG proposed a track A key comparison on pH of a borate buffer. Borate is a standard buffer listed in the EAWG strategy. The study was needed as a follow-up to K18.2019, for which some institutes were unable to provide results because of the SARS-CoV-2 pandemic. The coordinators were to be NMIJ and VNIIFTRI.

The EAWG additionally proposed a track C key comparison on pH of a phthalate buffer. Phthalate buffers are another key class of buffers and the study formed part of the EAWG strategy. The study would maintain support for many existing CMCs and provide support for new CMCs. The coordinator was yet to be determined.

PAWG proposed key comparisons on HbA1c coordinated by the HSA, LNE, NIM and KRISS, and on total haemoglobin in blood, and on Human Growth Hormone in serum, both coordinated by the PTB.

The meeting **approved** all of the proposed comparisons.

Dr Park congratulated the PAWG on moving to key comparisons from pilot studies.

14. REPORT FROM THE JCTLM

Dr G Miller reported on JCTLM activities. He noted that this was his first year as JCTLM chair and thanked his colleagues for their assistance in preparing the report.

JCTLM now included 60 member organizations, including the International Council for Standardization in Haematology (ICSH), as a member of the JCTLM Executive Committee.

The JCTLM maintained a database of higher order reference materials and methods, with a working group to review submissions. This was structured by analyte type, with review teams allocated to particular types of analyte. The number of methods and services continued to increase; the number of materials (currently about 250) had dropped recently, reflecting removal of materials no longer on sale. Metabolites and substrates formed the main category, including pure substances. Larger molecules, such as proteins, tended to include a smaller proportion of pure substances and more matrix materials.

The JCTLM Traceability, Education and Promotion WG was chaired by Dr Theodorsson. The group had been developing guidance documents to explain the practical implementation of the new standards ISO 17511, 21151 and ISO TS 20914, together with video materials to be published via the JCTLM website.

A JCTLM Members' and Stakeholders' online workshop on 'challenges in global standardization of clinical laboratory testing' was planned for December 2021. A further workshop on 'EQA/PT harmonization' was planned for December 2023.

JCTLM publishes a regular newsletter providing updates on database entries; the newsletter was published at the same time as the annual call for new entries.

A new task force on reference measurement system implementation, chaired by Prof. M. Panteghini (Milan), had been formed to provide practical guidance on implementing metrological traceability in laboratory medicine. The group had extended their membership to include major institutions involved in implementing traceability; developed recommendations for 13 common measurands; and prepared a synopsis of the main characteristics of higher-order materials and procedures listed in the JCTLM database. The preliminary results from the synopsis indicated that SI traceability was usually feasible for IVD manufacturers, given the scope of the requirement.

JCTLM was working to provide a new database structure, to provide (among other improvements) a machine-accessible interface for automated checking. Machine readability would rely on widely used existing standards, particularly JavaScript object notation (JSON) and XML. The aim was to make sure that any JCTLM database information could be imported directly into a users' own database (for example, a LIMS system).

Dr Miller reminded members that the closing date for submissions to the JCTLM database in 2021 is 31 May 2021. He also noted that to support World Metrology Day on 20 May, JCTLM would be presenting at least eight 5-minute video 'vignettes' on metrology in laboratory medicine.

In closing, Dr Miller drew attention to a recent call for experts to contribute to the JCTLM Quality System and working groups. He also noted that the revision of ISO 15194 and ISO 15193, on requirements for reference materials and reference procedures respectively, would require changes to the JCTLM quality manual in due course.

In discussion, Dr Swart asked whether there was an official representative of CCQM in the JCTLM Task Force on Reference Measurement System Implementation (JCTLM-TF-RMSI) to align the activities of JCTLM and CCQM. Dr Wielgosz said that there was no single official representative, but that membership included NMI members who did contribute actively to CCQM, ensuring good use of CCQM expertise.

In response to a question, Dr Miller explained that the workshop in December 2021 is aimed at addressing challenges in reference materials production. It would cover some technical issues such as commutability requirements and studies for clinical reference materials. The workshop would also consider regulatory challenges caused by different regulations in each country. This made production and certification of *in vitro* devices expensive because many different certifications were required, in turn impeding harmonization because manufacturers were reluctant to change procedures developed to meet local regulations.

Dr Botha asked how the problems of lack of commutability could be addressed. Dr Miller explained that many materials used for calibration and control showed lack of commutability with human samples and noted that IFCC had recently published a number of recommendations for assessment of commutability. Dr Wielgosz noted that CCQM currently had no specific processes for looking at commutability and suggested joint activity between CCQM and JCTLM would be useful in this respect.

Dr Li asked whether published CMCs were taken into account when evaluating proposed JCTLM services. Dr Wielgosz, in his capacity as executive secretary of JCTLM, explained that CMCs were taken into account for reference measurement service provision. However, JCTLM used ISO 15194 requirements for reference materials, and a CRM within a CMC listing that had not been demonstrated to have ISO 15194 compliance, currently would need to be verified in the JCTLM review process. He said that the JCTLM quality group was looking at this issue and were looking for volunteers to join the JCTLM Quality Review Team to support these efforts.

In relation to the JCTLM report, Dr Arce Osuna (CENAM) asked how the JCTLM works with stakeholders to improve the traceability of clinical markers to the SI, noting that when a user requests information about traceability of commercial materials to the SI, the response is generally private information from the company. Dr Miller said that JCTLM provides feedback on submissions to the JCTLM database but did not otherwise work directly with IVD manufacturers. In discussion, Dr Gillery said that IFCC had an IVD manufacturer working group with about 50 members. They were very much aware of the need for procedures to guarantee traceability to the SI and were keen to work with external stakeholders for help.

15. QUESTIONS ON WRITTEN REPORTS/RECORDED PRESENTATIONS FROM REGIONAL METROLOGY ORGANIZATIONS

Reports had been received from AFRIMETS; APMP; COOMET; EURAMET; GULFMET; and SIM (see CCQM/21-4,24,32,33,34)

Some questions had been submitted in advance and were discussed.

The AFRIMETS representative was asked in which sectors and countries Metrology in Chemistry activities were developing or likely to develop in countries outside of those mentioned in the report

(South Africa, Kenya, Egypt and Tunisia). Dr Botha said a number of countries had good potential to be involved (for example, Botswana, Mauritius, Uganda, and Tanzania). She added that several countries had large mining operations and would be interested in developing measurements for minerals exploitation and environmental monitoring.

The APMP had strong growth in the number of Chem-Bio CMCs in their region in 2017-2021, and the representative was asked how this was expected to evolve in the near future. Dr Inagaki, for APMP, said that many institutes were shifting to broader CMC claims so that the number of new claims was expected to reduce. In response to a further question, Dr Inagaki said that there were no current plans to change the present sector focus groups within APMP.

COOMET were asked whether there were any initiatives to launch sector specific focus Groups within COOMET. Dr Kustikov said that COOMET would like to increase focus group activity and COOMET planned new focus group activity in climate change and for energy.

The EURAMET report noted the formation of several new European Metrology Networks and Dr Wielgosz asked how these were expected to interact with the EURAMET TC-MC and eventually the CCQM. Dr Vaslin (Chair, EURAMET TC-MC) said that the metrology networks were still developing, but that the focus of the networks was on engagement with stakeholders, while the scientific committees focused on technical matters. Nonetheless, she felt that the added opportunities for stakeholder engagement would be of benefit to the metrology community in the longer term.

Dr Wielgosz asked about the SIM project on Toxic Elements in Amazonian Fish. Dr Cunha, for SIM, explained that the project was supported by PTB with assistance of NRC Canada and other institutes, and covered several major SIM economies. The project would improve capability for preparation of reference materials, particularly in relation to contamination in the Amazon basin.

Dr Park asked RMO representatives how the RMOs viewed the idea of ‘broad scope CMCs’. Dr Inagaki (for APMP) said that all claims had to be carefully considered. In the case of OAWG the claims had been discussed in considerable detail; by comparison the IAWG claims were relatively new for APMP. EURAMET had submitted a small number of broad scope organic and inorganic claims; these were in discussion. SIM had started to consider broad scope claims from major NMIs, but the majority of newer NMIs were submitting traditional CMCs with narrow scope.

16. QUESTIONS ON WRITTEN REPORTS/RECORDED PRESENTATIONS FROM INTERNATIONAL ORGANIZATIONS IN LIAISON WITH THE CCQM

Reports had been received from the International Atomic Energy Agency [IAEA] [CCQM/21-26]; International Federation of Clinical Chemistry and Laboratory Medicine [IFCC] [CCQM/21-25]; the International Union of Pure and Applied Chemistry [IUPAC] [CCQM/21-02]; ISO REMCO[CCQM/21-03]; and the Cooperation on International Traceability in Analytical Chemistry [CITAC] [CCQM/21-07].

Participant questions on the reports were invited.

IAEA Report

Dr Wielgosz noted IAEA’s project on development of CO_2 reference materials for calibration of infrared laser spectroscopy instruments for CO_2 isotope ratio measurements and asked how NMIs

could assist. Dr Groening explained that the activity was in collaboration with WMO. He said that both high accuracy and routine measurements were needed, and that for high accuracy measurements, NMIs could be of immense help. He also noted that IAEA had long cooperated informally with the CCQM IAWG and were seeking to formalize the arrangement. For routine work, robust, easily deployed measurements were needed but, outside Europe, transport of high-pressure gas standards is often impeded by safety and customs restrictions. To help overcome this, IAEA were supporting a workshop on RM production which he hoped would promote development of alternative standards that were easier to transport.

In response to a further question on IAEA plans for CMCs to cover the CRMs they produce for inorganic and organic analytes, Dr Groening said that much of the work was done in the agency's marine laboratories and they were currently seeking accreditation. He hoped that once this was in place, the Agency would be in a position to submit CMC claims and would then consider the submission route, including the appropriate RMO.

IFCC report

In response to a question for IFCC, Dr Gillery said that the development of reference methods for molecular diagnostics, particularly SARS-CoV-2, had been discussed in the IFCC Covid-19 task force, but there were no current plans for IFCC to develop reference methods. Dr Huggett added that he anticipated a number of JCTLM reference method submissions for SARS-CoV-2 from CCQM NAWG members.

IFCC were asked about the process for review and revision of IFCC methods. Dr Gillery said that this was an emerging issue for IFCC and explained that the first step is the identification of the need for revision. A project proposal would then be submitted to the scientific division to commence revision, which would form or delegate a working group to carry out the work. In response to a further question, Dr Gillery said that IFCC worked with other organizations, including NMIs, to develop RMs; for example, a haemoglobin A2 material was currently in progress to support thalassemia diagnosis. IFCC also had a new WG on human growth hormone and Dr Gillery hoped that the proposed CCQM study would provide a useful contribution. He added that the study coordinator is also a member of the IFCC working group on hGH, so a strong link was already established.

IUPAC report

Dr Wielgosz said that the draft IUPAC guidelines on organic purity were a good example of CCQM-IUPAC complementary work. He asked what other joint or related activities with CCQM would IUPAC like to undertake. Dr Mester (president, IUPAC AD) said that the guideline was in the final stage of the IUPAC consensus building process and should be published in 2021. In addition, IUPAC is undertaking a project to develop an internationally based white paper on analytical chemistry education and chemical measurement in university curricula. Analytical chemistry teaching in university chemistry courses had declined, and IUPAC intended to document this and propose a response. This was particularly important because analytical chemistry formed the major occupation for chemistry graduates. IUPAC felt that the chemical metrology community could play a key role in this because of their almost unique focus on measurement.

REMCO report

In response to a question, Dr Botha (as ISO TC334 Chair) explained that, while REMCO had been disbanded as an advisory body, all of the work of REMCO had been transferred to a new ISO

Technical Committee, ISO TC334. The structure of the new TC had been formed to mirror that of REMCO. Under ISO procedures, liaisons automatically lapsed on dissolution of committees, but liaison bodies could now apply for liaison with TC 334 using the normal ISO process. Similarly, ISO TC 334 would be making formal applications for liaison as needed to replicate the REMCO liaison structure, though she noted that it was often most efficient if a single individual acted as liaison representative in both directions. In response to a further question, Dr Botha said that TC334 had considered stakeholders other than NMIs and other ISO TCs, noting about 16 existing liaison relationships with ILAC, IAEA and others. She hoped that IFCC might also consider joining in a liaison capacity.

It was noted that REMCO and VIM definitions were sometimes different, and the REMCO report indicated that REMCO were working on alignment of CRM and RM definitions with the VIM. Dr Botha noted that with a new draft of the VIM, the introduction of a separate set of VIM definitions for qualitative ("nominal") properties, full harmonization with current REMCO definitions had not become simpler. However, REMCO (now TC334) were monitoring the VIM development and provided one of the ISO members on the VIM working group.

CITAC report

Dr Güttler reminded CCQM members that CITAC were again running an online seminar on 7 May 2021 covering the CITAC awards for 'best paper on metrology in chemistry' and hoped they would find time to attend; he also congratulated the CCQM members honoured by the awards.

17. CCQM MEETINGS

17.1. Arrangements for CCQM WG meetings to be held in 2021 and 2022

Given the uncertainties in travel for the remainder of 2021, there was no plan for a coordinated meeting later in the year. Working groups were encouraged to continue working online to progress their technical work.

17.2. Arrangements for April 2022 CCQM meetings

The April 2022 meetings were to be held in the week 25-29 April 2022, in person at BIPM if possible. The plenary would be held on the last two days of the week (28th-29th) if travel restrictions permitted a meeting in person. Working groups were expected to meet on 25th-27th April.

17.3. Proposals for CCQM/BIPM Workshops/ Webinars 2021-2023

Dr Wielgosz listed five candidates for future workshops and webinars. These included

- NMI preparedness for infectious disease pandemics

- Microplastic standards and metrology
- Particle metrology
- Support for accredited RM producers
- Particle counting and nucleic acid methods for virology

A workshop on NMI pandemic preparedness was agreed. H. Li (NIM), M. Tarlov (NIST), L. Dong (NIM), J. Huggett (LGC), Y. Bae (KRISS), C. Gonzalez (NIST) and R. Paroli (NRC) offered to assist on the organizing committee. Dr Güttler would provide support from PTB, Dr Lippa would seek support from NIST, and following consultation, Dr Braybrook (LGC) offered to lead the steering committee that would organize the workshop. NRC also offered support.

Dr Mackay felt that an internal CCQM workshop on microplastics might be feasible. IUPAC and NIST indicated support. Dr Mester noted that IUPAC were currently running a major project on the subject, covering nomenclature, chemistries and methodologies. Dr Wielgosz suggested that April 2022 might be a practical time to run a virtual workshop. Dr Mackay agreed to lead on the organization of the workshop.

The topic of particle metrology was considered. Dr Winchester suggested that individual WGs cooperate to arrange a joint workshop on particle metrology. This was agreed. Dr Winchester agreed to coordinate the event.

Dr Wielgosz agreed to consult with the CCQM SPWG and prepare the scope for a workshop or other event on CCQM support for accredited RM producers.

The possibility of a workshop on particle counting and nucleic acid methods for virology was discussed briefly. Dr Campbell was requested to consider further and bring a proposal forward in due course.

18. CLOSING REMARKS

Dr Park thanked Dr Wielgosz and the staff at BIPM for their support for the meeting. He congratulated CCQM members on the considerable progress made over the year, particularly in view of the difficulties introduced by the Covid-19 pandemic and consequent restrictions. He expressed a hope that it would again be possible to meet in person in 2022 and thanked all members for their attention and their contributions to a valuable and effective online meeting.

DECISIONS AND ACTIONS FROM THE 26TH MEETING OF THE CCQM

1. The CCQM approved the report of the 25th Meeting of the CCQM.
2. The meeting agreed to form a CCQM Task Group to update CCQM KCRV estimation guidance, convened by Dr S. Ellison, with the terms of reference set out in document CCQM/21-08.
3. **Action**: Dr Botha to prepare a short list of procedural issues for harmonization, for the attention of the CCQM SPWG.
4. The meeting agreed to form a CCQM Task Group to develop a strategy for stakeholder engagement, and appointed Dr Brown as convenor.
5. CCQM **approved** the following Key Comparisons:
   - OAWG: Polar analyte in high protein food
   - GAWG: BIPM.QM-K2 and preceding pilot study, carbon dioxide in air
   - EAWG: pH of a borate buffer
   - EAWG: pH of a phthalate buffer
   - PAWG: Total haemoglobin in blood
   - PAWG: Human growth hormone (HGH) in serum
6. The meeting agreed to arrange a CCQM workshop in late 2021, on NMI preparedness for infectious disease pandemics. The steering committee would be chaired by Dr J. Braybrook (LGC) with support from Dr R. Josephs (BIPM). Invitations for the steering committee would include: Dr J. Huggett (LGC), Dr H. Li (NIM), Dr M. Tarlov (NIST), Dr L. Dong (NIM), Dr C. Gonzalez (NIST), Dr. Y. Bae (KRISS) and Dr R. Paroli (NRC).
7. The meeting agreed to run a virtual workshop on microplastics in April 2022 and requested that Dr Mackay lead on the organization of the workshop. **Action:** Dr L. Mackay
8. The meeting agreed to arrange a workshop on particle metrology, involving different CCQM WGs, and requested Dr Winchester to coordinate the event. **Action:** Dr M. Winchester
9. The meeting requested Dr Wielgosz to consult with CCQM SPWG and prepare a scope for a workshop or other event on CCQM support for accredited RM producers. **Action:** Dr R. Wielgosz.
10. The meeting requested Dr Campbell to prepare a proposal for a workshop on particle counting and nucleic acid methods for virology. **Action:** Dr J. Campbell.
11. **Action**: The rapporteur to draft “Decisions and Actions” document and “Report of 26th Meeting of the CCQM”.