

# Consultative Committee for Amount of Substance – Metrology in Chemistry and Biology

## Working Group on Organic Analysis: Strategy 2021-2030

### 1. EXECUTIVE SUMMARY

The external drivers for the OAWG work programme feed in from three main sectors: food, clinical, and environmental. The food sector has been the highest priority sector in recent years in relation to the focus of services being developed across WG members. This prioritization continues for this next period. Measurements related to three key classes of compounds related to food safety: mycotoxins, pesticides and veterinary drug residues, are a core focus for the group. Nutritional content parameters (e.g. vitamins, fatty acids), including in relation to mandatory food fortification, are also ongoing issues. Food processing and packaging migration contaminants (furans, phthalates, polycyclic aromatic hydrocarbons and mineral oil hydrocarbons) are important areas and present renewed priorities for manufactured food products. Food authenticity and adulteration issues are of growing importance for stakeholders, and these are likely to require multidisciplinary approaches across working groups.

The clinical sector has been and continues to be a long-standing OAWG focus area. The WG will liaise closely with the IFCC (refer to glossary on page 58 for acronym definitions) and JCTLM on the clinical aspects of the OAWG strategy to best align with stakeholder needs. Through such collaboration, we aim to maintain up to date projections of priority measurands in the clinical space including target uncertainties and matrices to feed into our comparison selection. Current priorities span over 10 orders of magnitude in concentration in serum and include many of the analytes we have historically covered such as cholesterol, creatinine and vitamin D. Newer priorities extend to low concentration analytes such as 17-beta-estradiol and to compounds of higher molecular weight ranges such as immunosuppressants. The clinical area is also shifting towards new sampling approaches such as via dried blood spots and new reference measurement capabilities to underpin these areas will require development. The capabilities required within the OAWG to underpin the clinical sector overlap to a great extent with those required by the anti-doping and forensic communities and the WG will ensure these sectors are also considered in our planning.

The prioritization of issues related to the environmental sector has increased in recent years, with growing global concerns related to a range of legacy contamination issues. Persistent Organic Pollutants (POPs), especially dioxins and dioxin-like PCBs are still important and only limited services are available from metrology institutes to support these measurements. Newer challenges focus on perfluorinated compounds (especially per- and polyfluoroalkyl substances (PFAS)), endocrine disruptor compounds and antibiotics and these will be a focus for model systems for our planned comparisons. Microplastics have become another area of international concern. The measurement issues associated with this class are complex and thus a multidisciplinary approach is likely to be required. Effective determination of these contaminants in the environment is challenging and this area overlaps with the broader measurement issues associated with manufactured materials. These can range from plastics used in food and beverage packaging, personal care products and medical devices, to numerous types of fluids and lubricants and thin-film coated energy devices. Only a limited number of institutes are active in these areas and they will be considered in planning our Track C comparison programme.

State-of-the-art purity assessment is a mainstay for the WG as they underpin capabilities for the provision of SI-traceable calibrator materials. These will continue to be a major focus for the Track A key comparison programme supported by the BIPM. There will also be an extension of the scope of comparisons into investigating analytes having a larger molar mass range (400-1000) g/mol, organic salts and compounds lacking UV-chromophores. The provision of comparisons that underpin capabilities for the provision of calibration solutions is similarly critical. This need is also reflected in the BIPM Track A comparison plans. It will be supported by Track C key comparisons arising from the BIPM Capacity Building and Knowledge Transfer Programme that supports the Metrology for Safe Food and Feed in Developing Economies and which will cover a range of calibration solutions for important mycotoxin analytes.

Track A key comparisons to underpin the suite of capabilities needed for matrix material related services form the third aspect of the core comparisons for the OAWG. The suite of ten matrix key comparisons planned for the next 10-year period have a strong focus on the food sector. Additional challenges in the matrix area cover measurands at ultra-trace levels that are increasingly encountered and present unique challenges.

Our suite of comparisons will also be planned to support the evolution of broad scope CMCs for the WG. We have a guidance document that covers the expectations for evidence required for differing “breadths” of CMCs. We will be examining areas where there is limited evidence to support broad CMCs and take this into account in our Track A and Track C plans. Ongoing liaison with the RMOs will be important. Several areas flagged as requiring specialized comparisons to underpin niche capabilities will be supported by the upcoming SIM BTEX in solution comparison and the EURAMET estrogens in water comparison. Core areas for the OAWG such as pesticides in food will be supported by a planned AFRIMETS pesticides in fruit comparison.

The advancement of measurement science in relation to OAWG activities will have a strong focus on a range of instrumental methods and their metrological application. The WG will continue its focus on quantitative Nuclear Magnetic Resonance Spectroscopy (qNMR) and expand this to cover evolving areas of application such as quantitative <sup>19</sup>F, <sup>31</sup>P and <sup>13</sup>C as alternative nuclei, 2D-qNMR and HPLC-qNMR. The utilization of high-resolution mass spectrometry for metrological applications will be another area of investigation for the WG. There will be a continued focus on developing metrology fundamentals across the WG. Workshops on measurement uncertainty approaches will continue to be a priority and will include issues such as combining data from multiple methods and the quantification of multi-component matrix materials.

Stakeholder engagement priorities for the WG will include maintaining and strengthening our liaison with international organizations and with committees in laboratory medicine, particularly the IFCC and the Joint Committee for Traceability in Laboratory Medicine. There will be a broader focus on ensuring effective input to ISO and its Technical Committees as relevant to the OAWG, such as TC 34 (Food Products, in particular the development of ISO/WD 24583 Quantitative nuclear magnetic resonance spectroscopy — Purity determination of organic compounds used for foods and food products). CCQM has had historical approaches from commercial and non-NMI CRM producers to participate in comparison activities. In conjunction with the broader CCQM, we aim to establish new links and develop existing ones with this community, including the accreditation bodies, in order to establish what the metrology community can offer, where possible, to ensure the traceability of these services and to better underpin the demonstration of capabilities. We hope to extend this more broadly to PT providers in general and to enhance their interactions with the metrology community and with the use of accuracy-based reference values.

## **2. SCIENTIFIC, ECONOMIC AND SOCIAL CHALLENGES**

### **Food Sector**

The food sector is vital for the global economy. It is a highly regulated sector and requires reliable measurements in order to ensure product safety, quality and compliance. Key drivers in this sector include National and International Food Policies, with legislation enforced to minimize food safety risks, ensure fair trade of food and feed, and provide protection of the consumer. Where no national legislative infrastructure/administration agency exists, testing requirements defer to the United Nations Food and Agricultural Organizations (FAO) CODEX Alimentarius, and to the CODEX recommended standard methods of analysis, developed through International Standards Organizations such as ISO and CEN and voluntary standards organizations e.g. AOAC. Furthermore, market access and brand protection remain major drivers of food safety. Implementation of new food legislation, as well as the upgrading of the capabilities

of food safety inspection agencies to comply with international requirements and guidelines, are priorities for most countries in developing regions.

The main stakeholders are the National (Agricultural, Health and Trade) regulatory agencies, accredited food testing laboratories, government-mandated food monitoring laboratories and industry. Stakeholder testing laboratories are required to assure metrological traceability across a very wide breadth of analytes in order to meet the requirements of ISO 17025. In developing regions this would be more readily achieved by increasing the availability of CRMs in each country or region, avoiding importation and reducing costs. Several OAWG-relevant challenges that have been identified in this sector include the provision of calibration solution CRMs to meet the requirements of ISO 17025 for metrological traceability and food matrix CRMs for validation and quality control. Production of these types of CRMs is a priority across a wide number of NMIs/DIs. An illustrative example is for mycotoxins where pure standards are less appropriate due to their toxicity and cost and users prefer standard solution CRMs. This work has been assisted through training received from the BIPM Mycotoxin Metrology Capacity Building Programme. This programme has significantly expanded the capability base in this area for developing economies. In addition several institutes are coupling their development of mycotoxin calibration CRMs to the production of relevant matrix CRMs.

There is also a lack of CRMs for a large number of combinations of food matrices with associated priority parent contaminants and/or their metabolites. The EU RASFF - the Rapid Alert System for Food and Feed – is a useful resource for highlighting the main challenges and difficulties in the food testing area. NMIs/DIs are responding to these evolving needs by developing broad scope measurement capabilities for organic compounds in diverse food matrices. As an example the number of potential pesticides is extensive and continues to grow, similarly, new contaminants continue to be identified. A significant challenge exists to provide traceability for this range of measurands. The demand remains for reference materials to support testing of regulated priority food contaminants (mycotoxins, pesticides and veterinary drug residues) in agricultural commodities such as grains, fruits and vegetables, animal (meat, poultry, fish) and plant (soy) proteins, dairy, honey, nuts and oils. The nutritional content parameters (vitamins, fatty acids), including mandatory food fortification, and food processing and packaging migration contaminants (furans, phthalates, PAHs, MOSH, MOAHs) are both important areas and present renewed priorities for demonstrating the compliance of manufactured food products with regulatory requirements. NMIs are also playing leading roles in providing traceable reference values for food proficiency testing schemes across this breadth of measurements, with PT providers moving away from the use of consensus values.

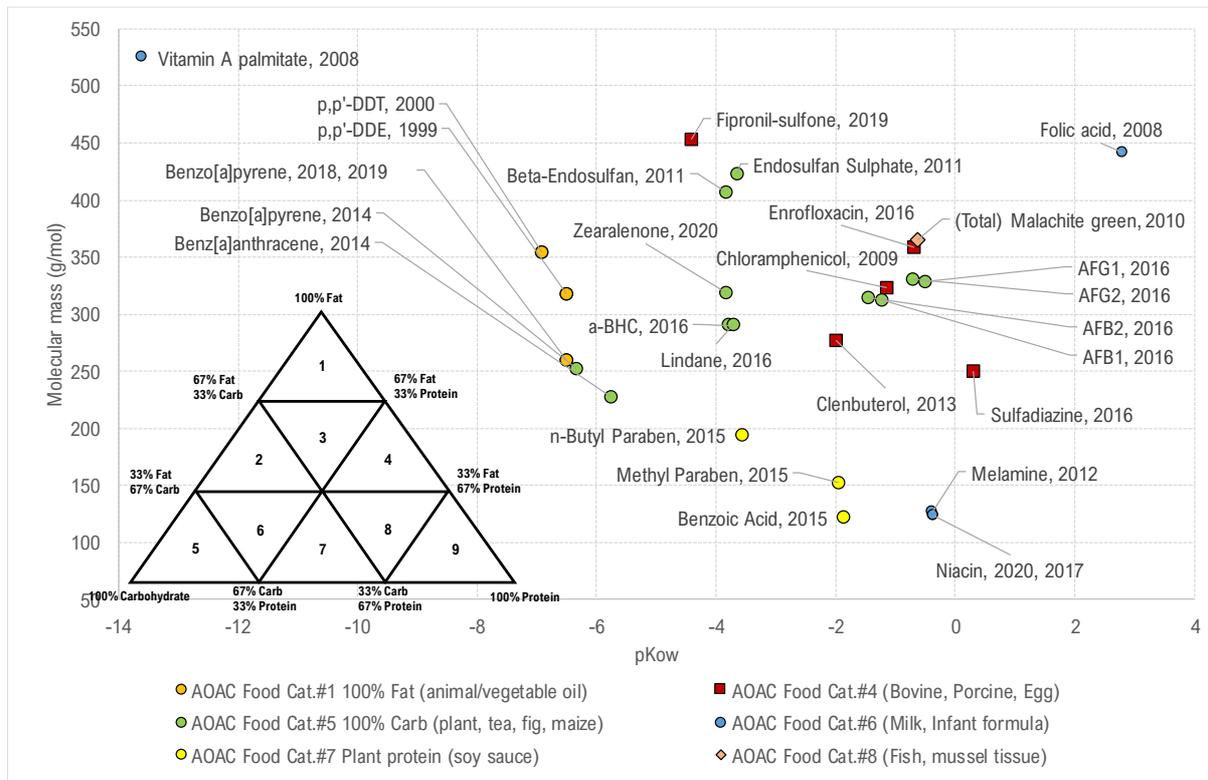
The development of accurate and reliable measurements for emerging food contaminants in diverse food matrices is also needed for toxicology studies and risk assessments to support new regulation. For example, fungal and drug metabolites, processing contaminants such as the PAHs, mineral oil saturated hydrocarbons and aromatic hydrocarbons (MOSH and MOAH), environmental contaminants such as halogenated flame retardants (PFOS and PFOA), microplastics and nanoparticles are also of great interest.

Measurement of novel food ingredients is a growing area. Analytical measurement challenges exist relating to the unique characteristics of a great diversity of indigenous food products and “superfoods”. The Regional Codex Committees are compiling new standards for unique foodstuffs that will require the development of reference measurements and reference materials. This includes countries with mandatory fortification regulations for staple foodstuffs that are not implemented globally (e.g. Vitamin A palmitate fortification of oil and sugar, in addition to grains).

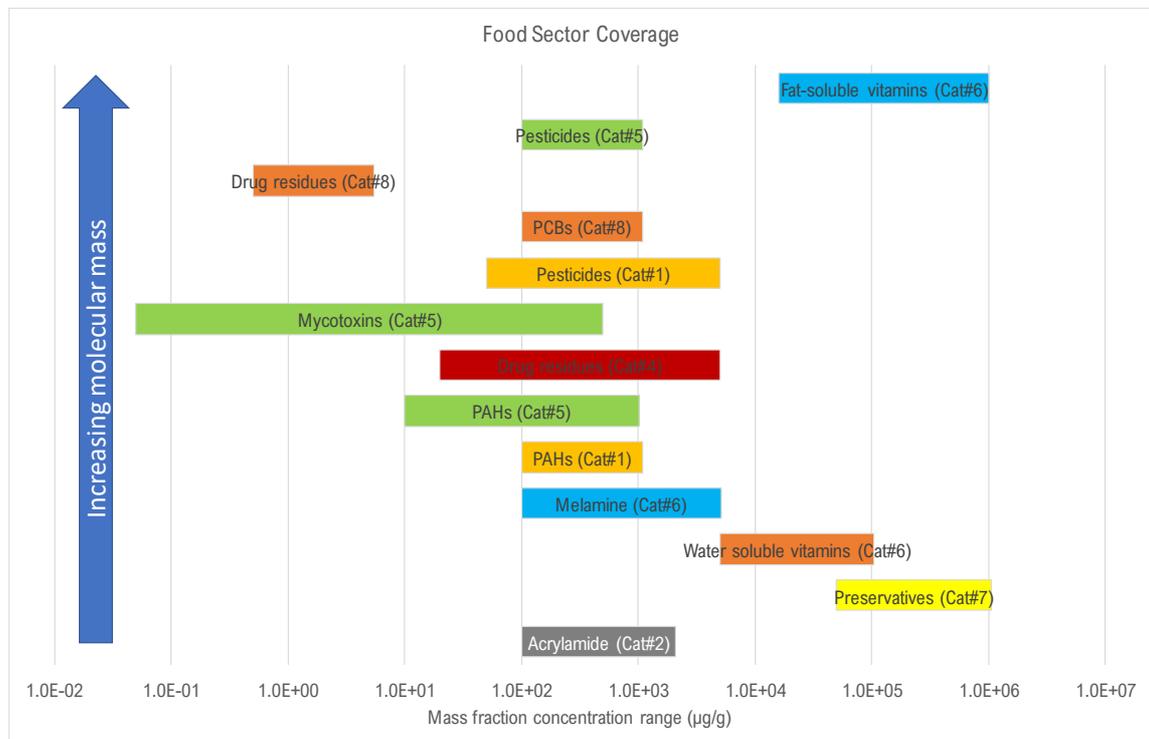
Qualitative analysis of food reference materials that involves identity confirmation of the analyte, especially when using LC-MS analysis, is yet another challenge. CRMs that can be used to validate the protein origin in processed foods (either vegetable or animal) in addition to issues of food authenticity/counterfeiting through fatty acid analysis, carbohydrate analysis and proteomic analysis are an emergent area of interest. Likewise, reference materials for use in the validation of methods to identify

contamination from food packaging and microplastics in foodstuffs also represent a significant future scan for the OAWG.

**Figure 1.** Summary of CCQM OAWG Food Key Comparisons and RMO Supplementary Comparisons to October 2020



**Figure 2.** Map of food measurement space covered to date, highlighting mass fraction ranges covered



**Figure 3** %RSD of participants vs. Log KCRV Mass Fraction  $\mu\text{g/g}$  (bubbles represent %U<sub>rel</sub> of KCRV)

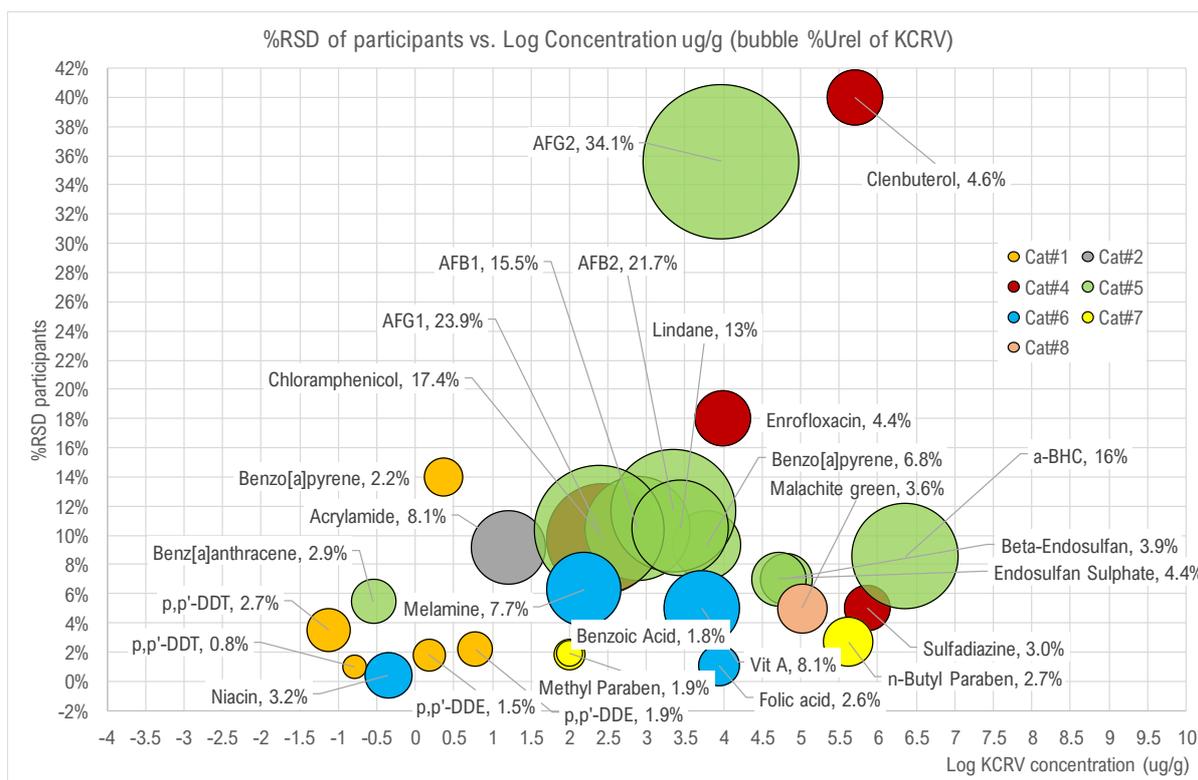


Figure 3 indicates that for some challenging analyte/matrix combinations (e.g. AFG<sub>2</sub>) the KCRV relative uncertainty and participant result variation were larger than our typical food sector measurements and would benefit from being reduced by undertaking further comparisons in these areas.

Several NMIs/DIs are participating in ISO technical committees to provide measurement science inputs for food and nutrition (e.g. ISO TC34), in addition to their National CODEX technical committees for food contaminants, nutrients and methods of analysis. There is also participation through voluntary standards organizations, such as the AOAC, within the various regional sub-sections that contribute to the development of new methods of analysis.

INRIM is working to develop a consortium for establishing a European Metrology Network on Food Safety through the Project “JNP-w04 Food Safety - Food-MetNet”.<sup>1</sup> This project aims to involve the metrology community, reference laboratories and regulatory bodies to address the need to harmonize standard operating procedures in order to provide standardized measurement methods and harmonized quality parameters to monitor food products along the food chain. If this project is funded, it could become a potential stakeholder for the OAWG. Recent<sup>2</sup> and upcoming<sup>3</sup> workshops related to food safety also provide a forum to identify stakeholder needs and align forthcoming NMI activities and programmes in this sector. The food safety workshop hosted by NIST in 2019 identified the following needs, which will be implemented through NIST and other NMIs/DIs short and long-term collaborative activities, for:

<sup>1</sup> European Metrology Network on Food Safety by the Project “JNP-w04 Food Safety - Food-MetNet

<sup>2</sup> AFRIMETS Food Safety Workshop (2018); NIST Food Safety workshop (2019) and subsequent reports: <https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.1251.pdf>; <https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.1252.pdf>

<sup>3</sup> LGC workshop (postponed until 2021); NMISA workshop (postponed until 2022)

1. Chemical contaminants: Incurred matrix RMs and PTs; Calibration materials (for metabolites and isotopically labelled substances); perfluoroalkyl substances (PFAS) in water and foods
2. Allergens: Support for a suite of complementary approaches through commodity and finished product RMs. In the EU, there are currently 14 priority food ingredients that require labelling due to allergies or intolerances. For 13 of these, it is the total protein content of the offending food/kg that is used as the measurand.
3. Authenticity & Adulteration: Authentic materials; Isotope ratio CRMs; Controls for rapid and handheld monitoring.

## Clinical Sector

For organic molecules, the clinical sector's need for metrological traceability is driven by the requirements for clinical laboratory medicine. The sector uses a vast range of measurements, from highly automated, high-throughput analysis to small-scale specialized measurements. The sector is served by large multi-national industrial corporations that provide entire *in vitro* diagnostic measurement services and solutions. As would be expected in a sector where measurement results have an often immediate and important impact on the health of a person, the sector is highly regulated (e.g. EU Regulation 2017/ 746 of the European Parliament and the Council on in-vitro diagnostic medical devices IVDR) and has internationally agreed quality standards for the metrological traceability of calibrators (ISO 17511), routine measurement services (ISO 15189), reference procedures (ISO 15193), reference materials (ISO 15194) and requirements for the competence of calibration laboratories (ISO 15195).

Historically a significant proportion of the OAWG effort has been focused on the needs of the clinical sector. A set of lipid and metabolite markers in serum were among the first measurands addressed by the OAWG. To date the group has completed seventeen key comparisons and six dedicated pilot studies in this area, which roughly equates to one study a year, intended to address the needs of the clinical sector. From the outset these studies were used by NMIs to hone their skills in preparing calibration standards, assessing new instruments and approaches for performing isotope dilution calibration procedures and in assessing and discussing their approaches to the estimation of measurement uncertainty. However, almost all studies have been in serum and only eight different measurands have been studied (cholesterol, creatinine, glucose, urea, uric acid, progesterone, cortisol and vitamin D). These have proven ideal for training, for assessing the impact of metrology in economic and societal terms, for guiding the NIST/SIM chemical metrology working group training opportunity<sup>4</sup> and for engaging the broader clinical community in CCQM activities. However reliance on comparisons involving such a small group of measurands will not provide the evidence of the broader range of capabilities needed for the analysis of more challenging measurands as required to address the evolving needs of the community.

Continuous organized efforts at a global (e.g. JCTLM, International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR)<sup>5</sup>) and at the local RMO level aim to coordinate the output and effort from NMIs to better achieve this objective. The OAWG should continue to support and take advantage of the opportunities that will arise from these initiatives, such as access to shared study materials. The clinical sector continues to become more metrology aware and as such many countries have well established regulated metrology infrastructures. Such an example is the "Guideline of the German Medical Association of Quality Assurance in Medical Laboratory Examinations" (Rili-BÄK) which stipulates the frequency of participation and maximum deviation permitted from the reference value for a group of priority measurands in biological fluids which must be achieved in order to provide measurement services in the clinical sector in Germany. The IFCC have set the expected equivalence of measurements from reference laboratories to be 25 % of the maximum deviation permitted by routine labs. This therefore establishes a "fit for purpose" criterion for the target uncertainty of calibrators and QC materials for the

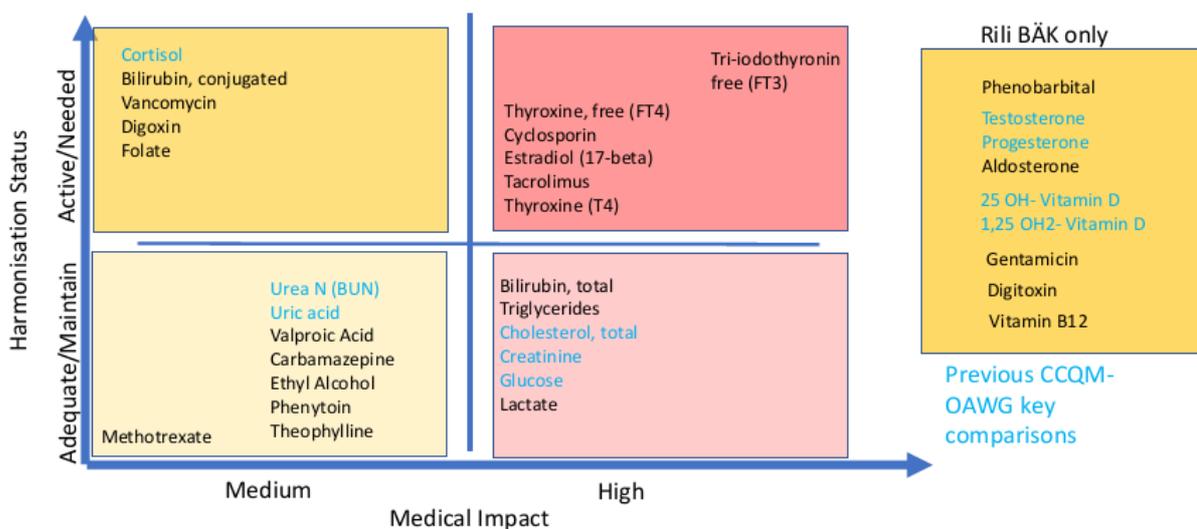
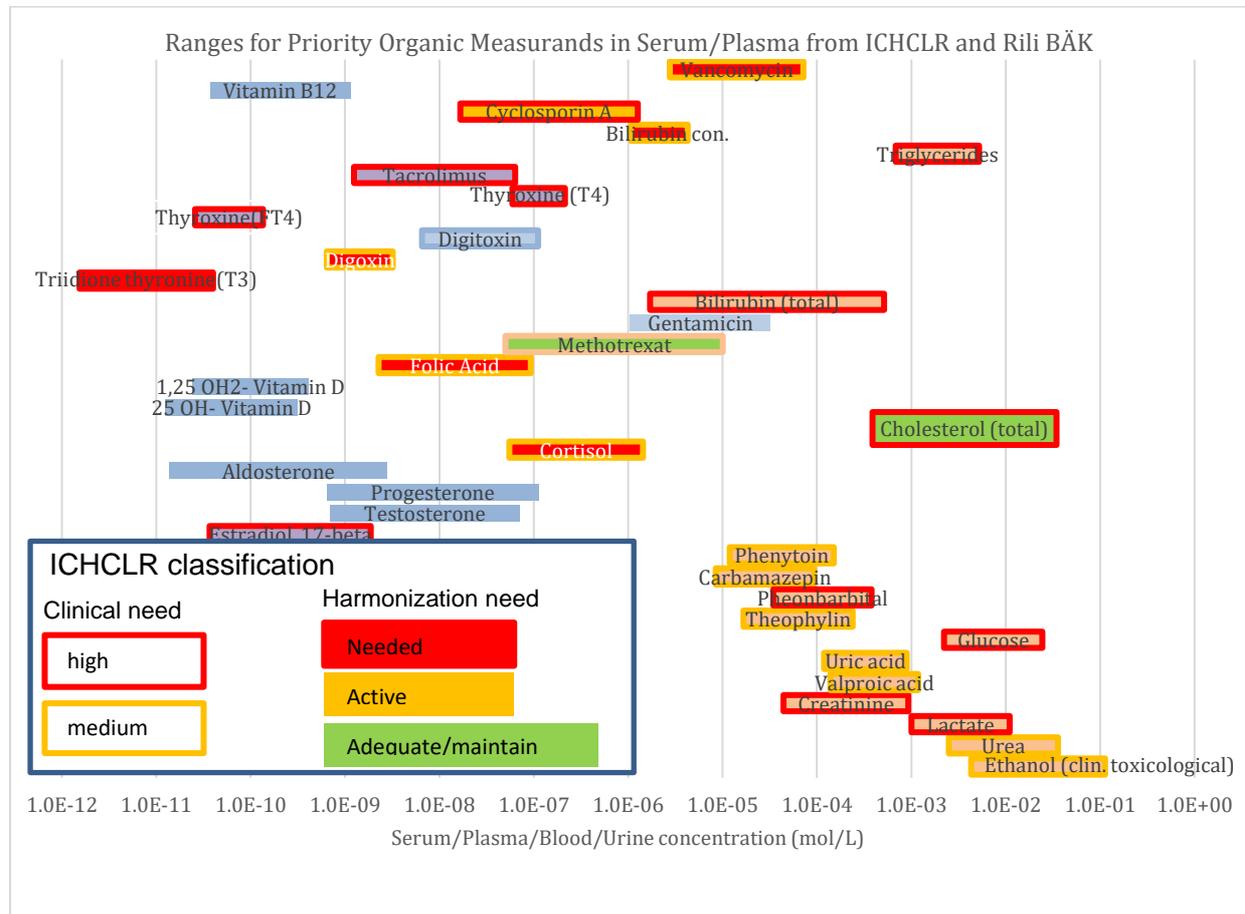
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<sup>4</sup> <https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.1209.pdf>

<sup>5</sup> <https://www.harmonization.net/>

sector. As these become more established, they should be used to assess the success of Key Comparisons and identify where improvement at the NMI level is necessary.

**Figure 4.** Map of clinical measurement space needs and OAWG comparison alignment



The current (as of 2019) Rili-BÄK list<sup>6</sup> contains thirty-five measurands that fall within the scope of the OAWG (Figure 4). These span over 10 orders of magnitude in analyte concentration in serum and range in molar mass from 50 to 1000 g/mol. The more recent additions to this list concern immunosuppressants and vitamins that are respectively in a molar mass and concentration range not previously covered by the

<sup>6</sup> Guideline of the German Medical Association of Quality Assurance in Medical Laboratory Examinations” (Rili-BÄK)

OAWG. Also, the new list contains requirements for dried blood spot analysis. These provide a particular metrological challenge as the volume of sample per unit area on the sample cards has a major impact on the measurement results. NMIs will need to adopt new capabilities to address the needs of the growing number of measurands that will be monitored via these methods.

NMIs must react to the needs of the community they serve, and this does not end at ensuring the traceability of a calibration service. The clinical measurement sector is innovative and seeks to use the most cost effective and specific methods of analysis. Ensuring that the calibrators and reference materials used are commutable is a continuous challenge. The high accuracy IDMS methods, which often require bespoke calibration standards and sample blends are labour intensive and prohibit the measurement of routine samples using the same procedure as that used for characterizing reference materials. New technologies for the automated gravimetric preparation of calibration and sample blends and the assessment of alternative methods of selectivity, such as high resolution and ion mobility mass spectrometry, may offer opportunities to address this need. The OAWG provides a unique space for exchanging experience in the assessment of such approaches. Organizing workshops addressing such innovations would be beneficial.

Finally, the drive towards precision medicine, digitalization of medical records and the use of artificial intelligence will influence new metrology needs. Precision medicine aims to provide a bespoke intervention based on how an individual is reacting to a treatment. The use of quantitative metabolomics and other “omics” methods in this and other sectors will require strategies for the calibration and quality assurance of these multi-parametric measurements.

Key activities proposed for the OAWG include workshops on new sampling techniques (such as dried blood spots), automation and commutability studies. It will be useful for the WG to maintain an up-to-date map of priority measurands in the clinical space including target uncertainties and matrices. This can feed into our comparison selection. It may be possible to make better use of efforts within the clinical and laboratory medicine community, engaging with EQAS providers and IFCC RELA for study materials if appropriate materials are available. We will seek feedback from the JCTLM and IFCC on the clinical aspects of the OAWG strategy to try and ensure we are best meeting stakeholder needs.

### **Forensic Chemistry and Anti-Doping**

Forensic chemistry covers a range of sub-disciplines and its practitioners are involved in activities as varied as the identification of drugs and poisons, analysis of drug metabolites, investigation of post-blast explosive residues, chemical warfare agents and fire accelerants. In order for the forensic chemist’s work to be of value to the justice system it must be based on sound metrological principles. Identification and quantification are the basis of the forensic chemist’s work and relies on the availability of appropriate CRMs. Forensic chemistry and by extension law enforcement agencies will for the foreseeable future be reliant on reference materials to ensure reliable chemical forensic evidence is presented to courts of law, both adversarial and inquisitorial. However, the availability of higher order CRMs cannot be taken for granted by the forensic chemistry community. For many years sufficient reference materials were available for use as standards in the identification of approximately 200 common drugs. Since 2009 there has been an explosion in designer substances with more than 1000 new drugs appearing in the market. Several NMIs/DIs have developed significant programmes to support this, however, the manufacture of appropriate reference materials has often lagged well behind their first identification. Similarly this has been an issue in forensic toxicology where drug metabolites for many of the new designer drugs are still not available. Metabolites for fentanyl derivatives, for example, are a current priority.

In the field of anti-doping there are similar challenges with respect to the breadth of reference materials that are required. The World Anti-Doping Agency (WADA) updates its Prohibited List annually; it covers classes of compounds such as steroids, stimulants, diuretics, narcotics etc. which represent hundreds of individual compounds. Many of the reference materials are needed as the metabolites of the parent compound and this adds to the complexity of producing these types of standards. The WG has a well-

developed programme to underpin pure organic calibration standards; ensuring that the future evolution of this series considers the issues associated with metabolites of drug materials, particularly conjugation and the associated formation of salt materials, will be required. A newer area for the anti-doping community is investigation of dried blood spot testing of athletes and several WADA labs are developing methods in this area and investigating mechanisms to improve the accuracy and comparability of the technique. The challenges in this area will be similar to those encountered by the clinical sector and the WG will need to consider future programmes to underpin the new services that will be needed from NMIs/DIs to support this new type of routine testing.

## **Environment Sector**

The environment sector continues to be a critical sector for the WG due to the reinforcement of regulations at the national and global level and also the growing interest of citizens in the quality of their environment at the regional level. The environment sector is mainly driven by regulation aiming to protect human and environmental health. The vast majority of regulation is developed at the national or regional level to meet local challenges. However, they echo internationally established guidelines, including the WHO guidelines for air and water quality. In addition, this resource is enhanced by international conventions signed by the great majority of states - notably the 1998 Aarhus Protocol on Persistent Organic Pollutants (POPs); the 2001 Stockholm Convention on Persistent Organic Pollutants; the Convention on Biological Diversity, and the Strategic Approach to International Chemicals Management.

Measurement challenges related to historical pollutants such as POPs; especially the 17 toxic congeners of PCDD/PCDF (Dioxins) and dioxin-like PCBs are still important, with newer challenges including chemicals of very high concern and very persistent substances (e.g. perfluorinated compounds as per- and polyfluoroalkyl substances (PFAS) and organometallics). Endocrine Disruptor Compounds (EDCs), commonly found as additives or flame retardants, and also antibiotics are of growing importance – aligned to the World Health Organization One Health concept - because they are recognized as a threat to biodiversity and human health. Last but not least due to high societal demand resin additives and microplastics, including nanoplastics, have become critical areas of concern. These issues call for horizontal cooperation between relevant Consultative Committee working groups and the major stakeholders to define the priority needs and build an agenda and roadmaps for priority programmes. At the ISO level a Joint Working Group between ISO/TC 147 "Water quality" and ISO/TC61 "Plastics" will be established to develop a standard on microplastic measurements in water. One other important issue arises from the need to demonstrate measurement capabilities at ultra-trace levels approaching method decision limits or at mass fraction levels where substances actually have limited effect. As an example, the natural estrogen 17-beta-estradiol and the synthetic one, 17-alpha-ethinylestradiol, which are currently of considerable focus within the environmental community, have a "Predicted no-effect concentration" (PNEC) of 0.4 ng/L and 0.035 ng/L in surface waters, respectively. The ability to undertake reliable low-level measurements of these analytes needs to be demonstrated. Finally, the use of effect-based monitoring (EBM) approaches is another growing area of concern as they are foreseen to enter into force in regulation.

LNE is working to develop a consortium for establishing a European Metrology Network on Pollution Monitoring through the Project "JNP-w03 POLMO". The aim of this project is to accelerate the creation of an EMN on pollution monitoring focusing on chemicals and radionuclides, where knowledge, needs and services are identified and easily accessible by the metrology community and the relevant stakeholder communities. The project will enable the European NMI/DI community to create a new approach to address their stakeholders' challenging requirements. If this project is funded, it could also become a potential stakeholder for the OAWG.

It will be important for the WG to engage in dialogue with our key stakeholders to ensure we are developing programmes that meet their needs. For complex issues such as the measurement of nano- and micro-plastics this will require a multidisciplinary approach involving collaborative work across a

number of CCQM WGs. This will be a priority area for workshops to share knowledge and assess the most effective responses by the metrology community. Other areas proposed for OAWG workshops in this sector are method validation at very low level of concentrations and qualitative measurements. The two key areas currently for the sector are perfluorinated compounds and EDCs (e.g. steroids hormones). These priorities should also be taken into account when selecting key comparison model systems.

## **Manufactured Materials and Industrial Products**

Organic-based manufactured materials and industrial products represent a mainstay for our global economy. Such products need to be appropriately evaluated to ensure that they are both suitable for their intended use as starting materials and feedstocks but also safe for consumers in their finished form as commercially available products. These products are ubiquitous and can range from industrial plastics for use in food and beverage packaging, personal care products and medical devices, to numerous types of fluids and lubricants and thin-film coated energy devices. The environmental and toxicological impact of these materials, their precursors and their eventual end-stage forms are also of concern and have significant implications for development of the circular economy.

*Analysis of Microplastics as a Future Challenge.* Microplastics (MP) are defined as synthetic polymer particles that range in size between 5 mm and 100 nm, where 100 nm is considered to be the border with the nanoparticle range. Due to their polymeric and particulate nature, microplastics differ considerably from the distinct and smaller size (< 1000 g/mol) analytes that are the typical focus of the OAWG. Relevant MP properties of interest to the analyst in a given matrix are:

- polymer type
- number of particles, particle sizes and size distributions as well as particle shapes
- total mass fraction of MP/polymer
- specific properties of individual particles (e.g. surface structure, ageing status)

The two most common analytical methods<sup>7</sup> that are currently available for the characterization of MPs are (1) FTIR and Raman spectroscopy for imaging to identify polymer type and to determine particle dimensions and aging status and (2) thermoanalytical procedures based on pyrolysis or combustion followed by GC-MS for identification and quantification of the volatile pyrolysis products of the polymer. The latter requires an authentic sample of polymer for use as a reference standard.

Spectroscopic procedures for MP analysis in complex environmental matrices<sup>8,9</sup> require laborious steps to concentrate the MP content prior to measurement and to remove interfering matrix components. The subsequent instrumental analysis tends to be tedious and the overall procedure has limited potential for automatization. Thermoanalytical procedures on the other hand often require minimal sample preparation and an automated version is commercially available. Although GC-MS quantification of volatile pyrolysis products may appear similar to procedures that have been the subject of OAWG comparisons, it should be noted that so far there is no appropriate labelled polymer available, and that currently MP quantification is based on external calibration and/or standard addition using the respective native polymer.<sup>10</sup> However, even with available labelled internal standards, establishing the SI-traceability of measurement results is likely to be a challenge for a procedure that is based on pyrolysis of a polymer.

Spectroscopic and thermoanalytical procedures should be regarded as complementary to each other in

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<sup>7</sup> Elert, A., Becker, R., Duemichen, E., Eisentraut, P., Falkenhagen, J., Sturm, H., Braun, U. Comparison of different methods for MP detection: What can we learn from them, and why asking the right question before measurements matters? *Environmental Pollution* 231, 1256 – 1264 (2017)

<sup>8</sup> Wu, M., Yang, C., Du, C., Liu, H. Microplastics in waters and soils: Occurrence, analytical methods and ecotoxicological effects. *Ecotoxicology and Environmental Safety* 202, 11090 (2020);

<sup>9</sup> Zhou, Y., Wang, J., Zou, M., et al. Microplastics in soils: A review of methods, occurrence, fate, transport, ecological and environmental risks. *Science of the Total Environment* 748, 141368 (2020).

<sup>10</sup> La Nasa, J., Biale, G., Fabbri, D., Modugno, F. A review on challenges and developments of analytical pyrolysis and other thermoanalytical techniques for the quali-quantitative determination of microplastics. *Journal of Analytical and Applied Pyrolysis* 149, 104841 (2020)

that thermoanalysis provides a rapid overview on type and mass fractions of polymers present in the matrix while spectroscopic procedures may be used to investigated particle size distributions in samples identified as being relevant by thermoanalysis.

Preliminary interlaboratory comparisons on MPs revealed poor comparability among different analytical approaches. At the ISO level there has been considerable discussion on this cross-cutting issue. International standardization of MP determination in environment matrices is currently being implemented in ISO TC 61. A project for developing standards for MP determination in food has also been accepted by the German Institute for Standardization (DIN). The normative project PR ISO CD 24187, *Principles for the development of standards for investigation procedures of plastics in environmental matrices and related materials* is also in the pipeline. Analytical method development in this area is currently very dynamic and further principles such as SIMS-ToF-MS or approaches for the characterization of specific types of polymeric materials are likely to be introduced.

The area of microplastics may not formally sit within the OAWG terms of reference, but it is recognized as a growing area of international concern and as flagged in the environmental sector strategy a multidisciplinary approach will be needed and workshops in this topic will be a future priority. This issue extends to nanoplastics and the challenges associated with the analysis of plastic residues having smaller particle size.

Other more traditional analysis areas related to polymers and related manufactured products is a priority for individual institutes having programmes addressing these. The OAWG will need to consider undertaking Track C type comparisons to ensure that these capabilities are effectively underpinned.

### **3. VISION AND MISSION**

#### **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 responsibilities of the CCQM are:**

- a. to demonstrate the global comparability of chemical and biological measurements, promoting traceability to the SI, and where traceability to the SI is not yet feasible, to other internationally agreed references;
- b. to advise the CIPM on matters related to chemical and biological measurements including guiding international activities related to the definition and realization of the mole and advising on the BIPM scientific programme;
- c. to reach out to new and established stakeholders to promote the international measurement system and prioritize needs;
- d. to progress the state of the art of chemical and biological measurement science and act as a forum for the exchange of information about measurement research, technical programmes and service delivery;
- e. to contribute to the implementation and maintenance of the CIPM MRA with respect to chemical and biological measurements.

## 4. STRATEGY

### Strategic Aims

In line with the CCQM's vision and mission, the aims of the 2021 to 2030 strategy are:

- To contribute to the resolution of global challenges** such as climate change and environmental monitoring, energy supply, food safety, healthcare including infectious disease pandemics, by identifying and prioritizing critical measurement issues and developing studies to compare relevant measurement methods and standards
- To promote the uptake of metrologically traceable chemical and biological measurements**, through workshops and roundtable discussions with key stakeholder organizations, to facilitate interaction, liaison and cooperative agreements, and receive stakeholder advice on priorities to feed into CCQM work programmes.
- To progress the state of the art of chemical and biological measurement science**, by investigating new and evolving technologies, measurement methods and standards and coordinating programmes to assess them.
- To improve the efficiency and efficacy of the global system of comparisons for chemical and biological measurement standards conducted by the CCQM**, by continuing the development of strategies for a manageable number of comparisons to cover core capabilities.
- To continue the evolution of CMCs to meet stakeholders' needs**, incorporating the use of broad claim CMCs where applicable to cover a broader range of services and considering options to present these in a way that meets stakeholder needs and encourages greater engagement with the CMC database.
- To support the development of capabilities at NMIs and DIs with emerging activities**, by promoting a close working relationship with RMOs including mentoring and support for NMIs and DIs preparing to coordinate comparisons for the first time and promoting knowledge transfer activities including workshops, as well as secondments to other NMIs, DIs and the BIPM
- 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**, by prioritizing where new areas or issues should be addressed within the structure and evolving working group remit as required.

## 5. ACTIVITIES TO SUPPORT THE STRATEGY

### 5.1. PROGRESSING METROLOGY SCIENCE

In conjunction with the role of the OAWG in the demonstration of the global comparability within our measurement scope, the WG also provides a forum that allows for dynamic knowledge exchange between its members. A focus for the working group is discussion and engagement to progress state-of-the-art chemical and biological measurement science in areas important to members' measurement products and services. The OAWG will also plan to conduct select Track D pilot studies to explore topics related to metrology science, in addition to hosting technical workshops and engagement opportunities with other working groups and external stakeholders.

### Advanced Metrology for Measurement Services

The advancement of measurement science underpins the development of measurement services for each institute that participates in the CCQM OAWG. The core of the OAWG activities are demonstrating comparability for pure and solution-based calibration products and services that underpin SI traceability and the delivery of matrix material-based products and services for accuracy control and method validation. In many cases, the advancement of measurement science lags behind the development of new

services and ultimately the global demonstration of these capabilities. The OAWG aims to leverage the knowledge and expertise of other NMIs/DIs to build a stronger global metrology infrastructure for all the members of the OAWG.

*State-of-the-art Purity Assessments.* The strategic aim in this area is for individual NMIs/DIs to continue to benchmark, demonstrate and challenge their technical capabilities to assign the mass fraction content (“purity”) of the primary component in an organic material. Performance in the Track A “organic purity” key comparisons will remain the main mechanism for institutes to achieve this goal. The scope of these comparisons will expand the structural complexity space to cover organic analytes having a molar mass up to 1000 g/mol.

In addition, information reported on in-house value assignment by individual NMIs of primary calibrators for use in other Track A, Track C and RMO comparisons (e.g. matrix comparisons), can also be used to provide supporting evidence of the capabilities of individual NMIs for purity assignment. However, in these cases support for the associated measurement uncertainty claims is limited to that achieved for the overall comparison result. Comparisons arising from dedicated programmes supporting qNMR measurements will progress knowledge for that specific purity assignment technique.

Liaison with other CCQM WGs will be developed and maintained to ensure consistent use of information from their comparisons that are relevant to OAWG activities. These include activities within the EAWG on the active H<sup>+</sup> content of organic acids and bases by coulometric methods, the GAWG on VOCs and the PAWG on content assignment of peptides and proteins and the IRWG on isotope ratio measurements of organic compounds.

It is anticipated that the ongoing discussions and reporting of comparisons undertaken over the strategy period, and individual NMI publications resulting from these activities, will produce harmonized approaches for:

- combination of purity values obtained using independent methods, especially mass balance and qNMR, but also other techniques (DSC, titrimetry, coulometry) as they become more widely used;
- assignment of overall measurement uncertainty and reporting values at natural limits;
- reliable quantification strategies for related structure impurity content.

Broader activities at the international and national level will be undertaken to encourage stakeholder involvement and coordination with the OAWG programme. The aim will be to link NMI “best practice” for SI-traceable purity assignment to needs in specific sectors (e.g. pharmacopeias, commercial RM production, standards for use in environmental, food safety and clinical chemistry) and as necessary for the implementation by regulatory agencies (e.g. USP, EDQM, CODEX, EC, WADA,) and by accreditation bodies (e.g. ILAC MRA Signatories for ISO/IEC, ISO 17034, ISO 15194) of specific requirements for the value assignment of pure organic materials.

New technical challenges for purity assignment proposed for consideration by the OAWG, whether by workshop, pilot study or key comparison are substances with molar masses in the range (400-1000) g/mol lacking UV-chromophores, organic salts and the measurement of enantiomeric purity. BIPM will continue to act as the coordinating laboratory for Track A purity comparisons and, where requested, will take a lead role in specific stakeholder engagement and liaison. This could include hosting workshops on purity assignment for specific measurement sectors. The OAWG members will be expected to continue to provide guidance and input to BIPM for the selection of the measurands and the design of the format for these comparisons.

*Next Generation Measurements for Matrix Materials.* A large majority (85%) of OAWG members have indicated that Track A comparisons with matrix materials are considered of high priority and are critical for demonstration of capabilities and maintaining CMCs. It is also recognized that the new challenges for organic analysis measurement science for matrix materials involve robust yet accurate certifications for

multifaceted measurands (e.g., isomers, enantiomers) in a single matrix material. In addition, measurands present at ultra-trace levels (ng/g or pg/ $\mu$ L) that are commonly encountered in environmental, food safety and clinical diagnostics sectors also present unique challenges. A priority area for the demonstration of comparability for reference materials, PT scheme reference values and other measurement services are the determination of hormones and other biomarkers in biofluids, often at levels at pg/ $\mu$ L in blood and serum. Additionally, the measurement of excretion by-products of hormones, drugs of abuse and other trace-level pharmaceuticals in urine and environmental matrix materials, such as drinking water and wastewater, present similar challenges.

As new methodologies are being applied to the characterization and certification of matrix reference materials, the institutes leading their development have the responsibility of identifying and accounting for measurement biases that can potentially arise during value assignment and ultimately ensure the validity of the certification. Workshops have been held by the OAWG to examine this issue and will continue to be a priority. The issue of CRM commutability and translation of higher-order services to routine testing laboratories and fit-for-purpose field assays also remains a highly pertinent issue, especially for the application of clinical diagnostics CRMs used in a calibration hierarchy.<sup>11</sup> The OAWG aims to address this important area for clinical CRMs through initial technical workshop engagements with critical stakeholders, including JCTLM members.

*Reference Data as an Emergent Measurement Service.* As the OAWG pivots its strategy into new sectors such as metabolomics and non-targeted analysis for food, materials and environmental measurements, the data and metadata associated with reference material characterization lends itself to a measurement service in its own right. NMIs/DIs are anticipated to be producers of such reference data as trustworthy validated datasets, which can be used to calibrate, validate or challenge developments for data analysis, e.g. using machine-assisted (“artificial intelligence”) or multivariate approaches. In the age of digital transformation, standards composed of “reference data” are often mentioned; this measurement service represents an area of emergent interest for the OAWG.

Generated data within OAWG key comparisons and pilot studies are well-documented and are acquired meeting the highest quality standards, which makes them ideally suited to serve as reference data. Measurement uncertainty estimates are generally robust and traceability is ensured and thus a high confidence in the results is achieved. It may be desirable to have the possibility of the exchange of measurement datasets (as raw data) themselves, including all necessary metadata (with the respective software versions used to generate data) between participants to be used as reference data so that measurements and conversions can be traced. A recent example of such an activity is CCQM-P150.b in which several participants volunteered to share their individual raw NMR spectral data for re-evaluation using various data pre-processing techniques. The use of well-documented, open source and machine-readable formats for such data is highly desirable and the WG can learn from this type of interrogation of the raw data.

Select reference data can be evaluated on pertinent comparisons to explore requirements such as open and readable spectral data formats from a range of NMIs/DIs. It is also anticipated that requested reference data would also generally improve the quality and comparability of the OAWG's comparison studies, thereby encouraging the harmonization of core competencies among the institutes.

### **Instrumental Methods and their Metrological Application**

The evolution of modern instrumentation and novel instrumental techniques will impact on our selection of future key comparisons as we will need to ensure we are capturing the demonstration of

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<sup>11</sup> Miller, W.G., Budd, J., Greenberg, N., Weykamp, C. et al. IFCC Working Group recommendations for correction of bias caused by non-commutability of a Certified Reference material used in the calibration hierarchy of an end-user measurement procedure. Clin. Chem. 2020 <https://doi.org/10.1093/clinchem/hvaa048>

metrologically-sound capabilities using these evolving technologies. In some cases, priority areas for pilot studies and technical workshops will be identified to validate and further investigate these advanced approaches for organic analysis.

*Quantitative Nuclear Magnetic Resonance Spectroscopy (qNMR).* The WG has coordinated a series of pilot studies to progress the best practice implementation of qNMR and this will continue to be a highly important technique for the WG. To date these have focused on applications for small molecules. Purity assignment of more complex materials (e.g. peptides, oligosaccharides, oligonucleotides) by external standard qNMR (possibly jointly with the PAWG) may be a potential metrological application of qNMR that could be investigated in joint projects or as a pilot study. Some of the evolving areas of application for this technique relevant to the OAWG are 1) HPLC-qNMR, 2) Quantitative  $^{19}\text{F}$ ,  $^{31}\text{P}$  and  $^{13}\text{C}$  as alternative nuclei, and 3) 2D-qNMR.

For low purity organic compounds, the major challenge for qNMR is to mitigate biases associated with unresolved impurity peaks. While HPLC is an efficient method to remove structurally related impurities, there are several possible approaches for the application of HPLC with qNMR and the OAWG could work on studies to help determine the accuracy and comparability of different methods.

qNMR studies moving beyond proton to include  $^{19}\text{F}$  and  $^{31}\text{P}$  nuclei is of current interest to a range of institutes. Quantitative  $^{13}\text{C}$  NMR measurements using relaxation agents, especially for the polymer and petroleum industry, is one application. Quantitative  $^{31}\text{P}$  NMR analysis may be important for characterization of food products and human body fluids. Promotion of the development of ISRM (Internal standard reference materials) for  $^{19}\text{F}$  and  $^{31}\text{P}$  qNMR and ISRM containing more than one nucleus of interest (or perhaps of different chemical shifts to cover a wider range) for use in performing multinuclear qNMR analysis will be valuable.

Purity determination of 'low purity' (< 90% mass fraction content) samples is routinely done by qNMR using an internal standard. In such cases, the use of 2D NMR experiments (typically COSY, HSQC and HMB) to better understand the impurity profile and select an analyte signal that does not overlap with impurity signals is an important adjunct. 2D qNMR experiments can also be used for the quantification of analytes that present a higher spectrum complexity. By dispersing the NMR signals into the second dimension and exploiting the wide spectral width in the heteronuclear dimension, signals can be more readily resolved to give specificity of analyte signals. The fundamental problem with the use of 2D approaches is that the biggest advantage of 1D qNMR, its uniformity of response across analytes, may be lost and care must be taken to minimize these deviations and account for them in the uncertainty budget. Such bias can arise from factors including differences in  $T_1$  and  $T_2$  relaxation during the pulse sequence, non-uniform magnetization transfer due to variation in  $^1J_{\text{CH}}$ , and non-uniform excitation in the second dimension. These methods may however be extremely valuable for measurements of larger molecules and mixtures, where peak overlapping hinders the use of simple  $^1\text{H}$  qNMR measurements

The following activities on aspects of qNMR for the WG are suggested:

1. Technical workshop looking at external calibration (application to low purity samples, larger/complex molecules, sample limited applications).
2. Technical workshop on alternative nuclei
3. Promote development of RMs (internal standards) for  $^{19}\text{F}$  and  $^{31}\text{P}$  quantification and RMs containing more than one nucleus of interest
4. Technical workshop on purity assignment of larger/complex molecules (e.g. peptides, oligonucleotides) by 2D-qNMR and external standard qNMR, possibly with PAWG. Followed by assessment in comparisons.
5. Technical workshop comparing HPLC-qNMR approaches (e.g. internal standard recovery correction), followed by assessment via existing comparison programme where possible.

6. Workshops in partnership with other WGs or as part of existing events (e.g. PANIC qNMR summit)

*High resolution mass spectrometry (HRMS).* High resolution mass spectrometry (HRMS) is widely used across scientific disciplines relying on organic chemical analysis including food, environmental and clinical chemistry. These instruments (Time of Flight or Orbitrap) have high mass accuracy ( $\pm 0.001$  Da), high mass resolution (ratio of mass to mass difference  $\geq 20\ 000$ ) and wide mass range (simultaneous acquisition of ions (full scan) up to 2000 Da). Hyphenated with either liquid, ionic or gas chromatography HRMS offers both high selectivity and broad analysis specificity and can therefore be used for structure confirmation and identification as well as simultaneous determination of known analytes and untargeted screening of thousands of unknowns in complex matrices. They can also be used for quantitative measurement in their targeted modes.

Despite the growing use of HRMS much still needs to be done on the assessment of the overall techniques employed and examination of the comparability of results. An important consideration for the OAWG is the potential utility of HRMS in pure material, calibration solution and complex matrix reference materials development. The ability to detect and quantitate a broad range of analytes, impurities and matrix components in reference materials offers potential advantages not possible with other techniques. An example of application of this is in stability testing of materials. Another challenge to address is standardization of qualitative LC-HRMS methods for unknown identification both in terms of data acquisition, e.g., MANTA interlaboratory study led by NIST<sup>12</sup> or for bioinformatics data processing, particularly where spectral libraries/compound databases are concerned. Characterization of existing matrix reference materials using qualitative untargeted HRMS methods can enhance and extend the utility of these materials for end users.

The following two activities are suggested:

1. Consideration of opportunities presented by existing CCQM studies for assessment of general quantitative performance of HRMS hyphenated techniques and comparison of results of qualitative multicomponent untargeted methods in clinical, food or environmental samples.
2. Sharing of approaches and best practices for application of HRMS methods in metrology applications and certified reference materials development and characterization within OAWG. The potential for organizing dedicated workshops in this area should be considered.

*Compound Independent Calibration by ICP-MS or related technologies.* Compound independent calibration (CIC) for determination of organic compounds is an emerging approach in modern analytical chemistry. CIC is a quantitative technique that provides an elemental response independent of the chemical structure of the molecules containing the element. Inductively Coupled Plasma Mass Spectrometry (ICP-MS) is one of the most powerful analytical techniques for elemental detection with excellent sensitivity and selectivity. ICP-MS coupled with chromatographic techniques, already used for the characterization of trace level inorganic content, also provide the possibility for organic analysis and has been applied for organic analysis of materials containing Si, P, Br, S and elemental species. For traditional organic analysis, each compound needs a corresponding reference material or analytical standard. However, appropriate types of reference materials remain scarce.

The following activities are suggested:

1. investigating the use of CIC techniques during planned pure organic or standard solution comparisons using either an inorganic element or other organic reference material as the calibrator for primary component content assignment.
2. trialing of CIC quantification of organic compounds in matrix materials via GC/LC-ICP-MS.

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<sup>12</sup> <https://www.nist.gov/programs-projects/method-assessment-non-targeted-analyses-manta-program>

## Measurement Uncertainty in Organic Analysis Applications

The OAWG has surveyed the general approaches taken by member institutes for the assessment of measurement uncertainty. This effort includes exploration of traditional and novel approaches used to express confidence in results submitted for OAWG comparisons, as well as for the calculation of appropriate consensus estimates.

The strategic aim of this work is to ensure that results generated by member institutes are realistic and reliable indicators of measurement comparability. To achieve this goal, efforts will be made to establish procedures for OAWG verification of uncertainty estimates submitted during participation in OAWG comparisons, as well as general guidelines for considering likely sources of uncertainty. Furthermore, sharing and examination of specific procedures for estimating uncertainty can encourage use of approaches across the OAWG that are comparable and adequately rigorous. Such efforts will support the metrological utility of information from OAWG comparisons and thus benefit stakeholder interests supported by OAWG activities and member institute services.

Workshops have been conducted and proposed for the exploration of general approaches to estimating measurement uncertainty within the OAWG. These topics covered purity analyses and the measurement of chemical quantities in matrix substances. Although specific approaches to estimating measurement uncertainty depend upon technical procedures and experiment design, such workshops aim to establish general frameworks and recommendations for uncertainty that are appropriate for methods of measurement commonly used in organic chemical analysis. These workshops are intended to preface and promote discussion amongst the OAWG during assessment of comparison datasets and ensure that expressed uncertainties appropriately describe the measurand. Such critique is meaningful for both the determination of comparison consensus and the respective participant degrees of equivalence.

Comparison-specific discussions within the OAWG can be of similar format and combined with those routinely conducted for assessing the technical validity of submitted results. This typically includes examination of approaches used by participants that yield different results for the same measurand. Verification of dissimilar uncertainties reported by participants employing similar technical procedures will also be useful for ensuring valid datasets and assessing comparability. Measurement uncertainty workshops and comparison-specific discussion will require regular attention during OAWG meetings and additional effort by comparison coordinators and participants. Recommendations for rigorous approaches to consensus estimation and calculation of degrees of equivalence based on comparison results will be produced by a planned CCQM *ad-hoc* working group for the statistical treatment of comparison study data sets. These recommendations will be reviewed by the OAWG.

### Proposed Technical Workshops and Track D Pilot Studies

To address the evolving challenges faced by the WG a number of priority areas for workshops with a technical focus have been flagged. These were considered by the WG during the preparation of this strategy document and the higher priority topics were ranked for importance on a scale of 1 (lowest) to 5 (highest). The conclusions are presented in Table 1.

The topics are broken down into three themes:

- Advancing Measurement Techniques and Analytical Methods
- Metrology Fundamentals in Organic Analysis
- Sector-specific Metrology

In regards to advancing measurement techniques the highest ranked areas were investigation of the application high resolution mass spectrometry for metrological applications and continuing the discussions from the CCQM-P150 qNMR pilot study series, where the next proposed topic was assessing peak deconvolution software in more detail. Other aspects of qNMR analysis such as utilization of other nuclei were also highly ranked. The investigation of mass balance approach for pure substances with no

chromophores is another area of focus to ensure we assess current approaches for these types of compounds.

In regards to metrology fundamentals in organic analysis, measurement uncertainty approaches, including combining data from multiple methods, was the highest ranked topic. This follows on from a long series of uncertainty workshops the WG has coordinated and this remains a high priority. The second highest topic was multi-analyte quantification. This is becoming more and more important as services offering multiple analytes are desired by our stakeholders and establishing the most effective approaches to this is of wide interest. KCRV estimation approaches for key comparison data evaluation were also flagged as of interest for further discussion.

In regards to sector-specific metrology areas, food authentication and food safety was the clear highest priority. This was followed by commutability for clinical CRMs. This is likely to be a topic that may also be a cross WG priority. Within the clinical field new aspects such as the testing of dried blood spots will be a future issue for consideration as NMI/DIs develop services in this space.

The area of microplastics is one that is an important global issue and one which cuts across a range of CCQM WGs. This will be certainly be a topic for consideration during the first half of this strategic plan period.

In addition to co-ordination of OAWG or CCQM workshops an alternative approach that will be more fully utilized in the future is participation of OAWG members in external technical workshops and conferences with subsequent report-outs to the OAWG at-large.

**Table 1.** Priority areas proposed for Technical Workshops and prioritization results from OAWG members

Theme	Topic	Prioritization Score (out of 5)
Advancing Measurement Techniques and Analytical Methods	High resolution mass spectrometry (HRMS) quantification for high accuracy measurements	4.1
	qNMR studies:	
	a) Follow on to CCQM-P150.b – assessing peak deconvolution software on raw FIDs	4.0
	b) qNMR external calibration techniques	3.7
	c) Other nuclei (e.g. N and F)	3.7
	d) Newer modes of qNMR quantification (e.g., 2D, 13C-decoupling) and including low purity via HPLC-qNMR	3.4
	Investigation of mass balance approach for pure substances with no chromophores	3.7
Metrology Fundamentals in Organic Analysis	Quantification and uncertainty estimation for low level impurities in pure organics, e.g. Karl Fischer measurements near LOD	3.2
	Measurement of “blank” materials	3.2
	Advanced measurements with robotics	2.5
Metrology Fundamentals in Organic Analysis	Measurement uncertainty approaches, including combining data from multiple methods	4.5
	Multi-analyte quantification	4.3
	KCRV estimation approaches, in simple terms	3.8

	Traceability for qualitative determinations	3.7
	Improving accuracy with double-IDMS technique	3.5
Sector-specific Metrology	Food authentication and food safety	4.4
	Commutability for clinical CRMs	3.4
	Biotechnology	3.0
	Circular economy	2.5

The OAWG has leveraged Track D pilot studies to explore new analytical methods and measurement science challenges deemed important for NMI/DIs for developing new measurement services. In many of the areas flagged in Table 1, a preference was indicated to follow on from a workshop with potential assessment of capabilities via pilot studies. The sole focus of the WG during the last strategic plan period was centered on qNMR pilot study investigations to build further confidence in this technique as a primary ratio method for chemical purity assessments.<sup>13</sup> This area is still a priority focus, however Table 1 flags the key areas that our pilot study activity will potentially expand into.

A number of other areas have been flagged by the WG as possible pilot study topics:

- Technical challenges related to mass balance approach (e.g. salts, counter ions, no chromophores)
- Identification of unknowns (in pure chemicals and matrix materials)
- Automation in data generation and data processing (e.g. non-targeted analysis and screening approaches)
- Data processing comparisons of reference data sets
- Comparisons of bioassays to higher-order techniques

These topics will be considered by the WG in their planning of their comparison activities.

### Interactions with other CCQM Working Groups

Many areas of science are multidisciplinary and there are many areas where the OAWG will be best placed to work together with other CCQM working groups, or even across other consultative committees. In terms of interaction with other working groups, there are numerous topics to be considered over the period of this plan. The organic purity section above highlighted a number of areas where approaches from other WGs will be valuable to consider. There are a number of well-established analytical areas that overlap with the IAWG. The analytical methods required for the study of organometallics are traditional for both organic analysis (derivatization, LC-MS, GC-MS) and inorganic analysis (ICP-MS). The speciation of toxic elements, such as organic mercury in food and organotin in the environment, remain priority areas. The Council of the EU approved the EU Ship Recycling Regulation in 2013 which makes it mandatory for every ship to have an Inventory of Hazardous Materials (IHM) for 1 January 2021. This will make the determination of organotins compulsory and increase the profile of these measurements.

Amino acid analyses for protein quantification have been successfully explored as a major point of interaction between the OAWG and the PAWG. There is still a need for demonstration of global comparability of these analyses when applied to different and more complex systems such as larger proteins, with increased number of cross-links and post-translational modifications (PTM). Closely related to this, there is a growing need at the protein quantification level for the indirect determination of proteins by quantifying prosthetic (non-amino acid) groups. These can be applied to the quantification of large proteins such as hemoglobin that possess such groups in their composition. Another important observation is that the PAWG activities that interact with the OAWG have thus far prioritized analytes and

<sup>13</sup> CCQM-P150 report; CCQM-P150.b (Draft)

applications in the clinical area. Some economies, however, have great interest in protein analyses that relate to food, such as allergenic proteins. The OAWG could help the PAWG in planning new activities that would approach these issues.

Although the IRWG was only created recently, its first key comparison utilized an organic compound (i.e., vanillin) which serves as an indication of the great potential for interaction between these two groups. As a well-established WG, the OAWG can help the IRWG progress its activities in of the measurement of light isotopes. These applications will contribute to some of the issues in food authenticity, geochemistry, forensics and doping control that are also of interest within the OAWG. Isotope composition data of high-purity materials are also a potential area of interaction between these two groups. Finally, in terms of isotope ratio measurements, there is a growing need for site-specific determinations which rely largely on applications of well-established methods in the organic analysis field such as gas chromatography (coupled to Isotope Ratio Mass Spectrometry) and NMR. Developments in these fields within the CCQM will certainly depend on the cooperation between the IRWG and the OAWG.

Approaches to developing multi-analyte CRMs more effectively will be a possible discussion across WGs. There is a growing demand for this and learning from each other on the most effective techniques to deliver broader scope CRMs will be valuable. The emerging issue of the desire of stakeholders for materials certified as “free-from” particular analytes will be another area that warrants cross WG discussion. The legislative and analytical perspectives of this issue are important. Considering common approaches for measuring and estimating the uncertainty of "absence" is an emerging issue.

The importance of qualitative measurements for all chemical and biological sectors relevant to the CCQM was also identified, and the role of the CCQM in this area needs to be considered.

With regard to interactions outside of the CCQM, measurements of nano/microplastics are a growing area of concern and the techniques used for their analysis are very broad. This is likely to be a cross WG issue and also a topic for discussion with the Consultative Committee for Length (CCL).

## 5.2. IMPROVING STAKEHOLDER INVOLVEMENT

As an entity at-large, the OAWG has not had strong direct relationships with other external stakeholders. However, in the survey of members in March 2020 nearly half indicated the desire to strengthen these relationships with international standardization bodies and other metrology organizations. The classes of stakeholders relevant to the OAWG include:

- International organizations and bodies such as IFCC, WADA, Codex Alimentarius, national Pharmacopeias, IUPAC
- National government departments or agencies such as EPAs, US DEA, US FDA, ANSES (French Agency for Food, Environmental and Occupational Health & Safety)
- Regional legislative bodies such as the European Commission
- Metrology organizations such as JCTLM and RMO chemistry-based technical committees
- National, regional and international standardization and accreditation bodies such as ISO, CEN
- National and international trade or inspection organizations
- Industries across sectors such as food, environmental, clinical, forensic
- National and international professional organizations
- Scientific and technical bodies such as AACC
- Academic research institute (universities and laboratories involved in research translation)

The OAWG survey flagged suggestions for hosting workshops to educate chemical and clinical testing laboratories, and accreditation bodies, on the importance of accuracy-based PT programmes and metrological traceability, in addition to performing a needs and impact assessment of measurement services to identify where reference values provide critical value to PT schemes as well as priority CRMs for different sectors. Collaborations with other NMIs/DIs for training, PT schemes and CRM development has also been identified as an area for engagement.

Specific activities with international organizations (ISO, WHO, WMO, etc), Food and Agricultural Organization CODEX Alimentarius and the major pharmacopoeias regarding their roles in traceable measurement standards may also represent a growth area for the OAWG. Joint technical workshops with regard to the clinical, environmental, or food sectors, and regarding specific technical capabilities (e.g., qNMR spectroscopy) to discuss current analytical challenges faced by routine laboratories which impact on regulatory or trade decisions may represent another mechanism for engagement.

As an example of direct engagement with industry, the international metrology community has worked within the broader analytical spectroscopy sector to advance both qualitative and quantitative analytical methods for NMR spectroscopy. This includes participation within the ValidNMR Group<sup>14</sup> as part of the larger Practical Applications of NMR in Industry Conference (PANIC) and the qNMR-Summits<sup>15</sup> with the aim of international harmonization and validation of processes related to applications of qNMR spectroscopy. Through these efforts, both terminology and consensus-based approaches to NMR validation are to be developed and directed towards accreditation bodies for ultimate usage. In order to express the necessary commitment and trust of the stakeholders in qNMR spectroscopy, members of the NMI community (and the OAWG) are further encouraged to participate and provide guidance towards standardization efforts.

### **International Organizations and Committees in Laboratory Medicine**

The concept of Reference Measurements Systems (reference methods, materials and measurements services) is well developed in the field of Laboratory Medicine, and the IFCC has been a Member/Liaison Organization of the CCQM since 2000.

Currently, the only BIPM sector-specific standing committee activity is within the field of laboratory medicine and in vitro diagnostics (IVDs), with the Joint Committee for Traceability in Laboratory Medicine (JCTLM) established in 2002. The JCTLM maintains a database of higher metrological order reference methods, materials and services. Approximately 95% of the ca. 300 reference materials entries listed in the JCTLM Database are from NMIs, with the majority of the analytes falling within the OAWG terms of reference.

Requirements for the properties and documentation for Reference Materials intended for use in the laboratory medicine field have been developed by ISO TC 212/WG2, used by the JCTLM, and cover both accuracy and commutability. The CCQM OAWG comparison programme addresses accuracy of measurement procedures but has no activity that covers commutability studies. The lack of appropriate commutability data for reference materials to support their intended use statements can be a source of non-compliance with stated documentary requirements.

The IFCC, within its Scientific Division, has a Committee in Traceability in Laboratory Medicine (overseeing the RELA schemes of comparisons for Reference Measurement Services) and a Working Group on Commutability in Metrological Traceability. In order to strengthen liaison between the IFCC SD and the CCQM, the BIPM and IFCC signed a Memorandum of Understanding (MoU) in 2020, which will facilitate cross representation between the organizations.

The International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) is a relatively new grouping that was established following a 2010 workshop hosted by the AACC and NIST. Its mission is to provide a centralized process to organize global efforts to achieve harmonization of clinical laboratory test results, and strives to bring together interested parties to work together on the standardization of prioritized analytes.

Additional focus on OAWG involvement with IFCC and JCTLM would be expected to streamline the JCTLM review process for reference materials covered by CMCs, including replacement batches, as well as to optimize the CMC review processes so that both CIPM MRA and JCTLM requirements can be met when

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<sup>14</sup> <http://www.validnmr.com/>

<sup>15</sup> <http://www.qnmrsummit.com/index.htm>

needed. Engagement of the OAWG would also facilitate the development and implementation of best practice procedures for demonstrating commutability of CRMs and improve the synchronization of appropriate CCQM key comparisons with any relevant interlaboratory comparisons as part of the external quality assurance schemes for reference laboratories (EQAS for RELA).

At the CCQM level it has been suggested that an approach to achieve improvements in interactions between the IFCC and CCQM may be to establish a CCQM liaison to the IFCC and JCTLM. Topics suggested for consideration are establishment of a task group addressing commutability of reference materials in laboratory medicine, and other cross-cutting WG issues, as well as exploration of processes for improved interlinking of CCQM and RELA interlaboratory comparisons. Existing representation on IFCC committees could be better utilized to ensure two-way feedback. In conjunction with this, an approach to achieve improvements in interactions between the JCTLM and the CCQM OAWG would be to encourage NMIs/DIs active in the CCQM OAWG to nominate experts for analyte specific JCTLM Database review teams as vacancies arise. The OAWG members could also nominate an expert to join the JCTLM Quality Systems Development review team and contribute to and review outcomes of the JCTLM Task Force on Reference Measurement System Implementation (JCTLM-TF-RMSI). NMIs that are active in the CCQM OAWG would also be encouraged to participate in the biennial JCTLM Members and Stakeholders meetings.

### **ISO and its Technical Committees**

ISO technical committees develop written consensus standards, many of which describe or are related to chemical analytical measurement. The standards are developed by experts from National Member Bodies of ISO, active in working groups of the Technical Committees (TC). Nomination to participate as an expert in a TC or WG is via the National Standards Body. A number of NMIs have their own staff as members ISO TCs and WGs in this way. The BIPM can also apply to be a liaison organization to relevant Technical Committees and Working Groups and currently has Liaison A status with a small number of ISO TCs/WGs which deal with mission critical work items and written standards, for example: ISO REMCO (ISO 17034 relevance to the CIPM MRA); ISO TC 12 (ISO 80000 series on Quantities and Units with relevance to the SI brochure); ISO TC 212 (ISO 17511, 15193, 15194, 15195 with relevance to the JCTLM review process). In addition ISO REMCO is a Liaison Organization of the CCQM.

A number of NMIs and NMI experts that participate in the CCQM OAWG are also active within ISO TCS and WGs and contribute to the writing of standards on measurement techniques and analytes/measurands that are also the focus of CCQM OAWG activities, studies and comparisons. The participation of individual NMIs in ISO TCs and WGs provides a direct mechanism to ensure best practice in metrology is introduced into ISO standards. However, not all NMIs, and sometimes, only a few NMI experts, are active in ISO work, whereas there is a substantial interest in learning of these activities. In addition, ISO TCs and WGs provide an extended network of organizations and parties that are often very interested in the work of NMIs and could help in programme formulation and dissemination of information.

A specific involvement of OAWG members with ISO TCs and WGs would be expected to achieve 1) knowledge transfer to NMIs on the latest information on standards development of interest; 2) facilitate the organization of joint workshops between CCQM/CCQM WGs and ISO TCs/WGs on areas of mutual interest, reaching a broader group of stakeholders; and 3) ensure ISO written standards take into account the latest developments in metrology and reference measurement methods and metrological traceability. Through regular stakeholder involvement with the CCQM OAWG, anticipated results could include: 1) inclusion of a permanent agenda item for OAWG to cover ISO TC work items/standards of interest, 2) opportunity for NMIs to report on relevant ISO TC work items/standards they are contributing to, 3) consideration of current work items that may be mission critical and requires additional input or specific liaison to be established, and 4) prospects to organize joint events (e.g. webinar or workshop) with ISO TC/WG.

ISO TCs with work items of current potential interest in 2020 have been identified as:

- TC 34 (Food Products) (including ISO/WD 24583 (Quantitative nuclear magnetic resonance spectroscopy — Purity determination of organic compounds used for foods and food products); projects on aflatoxin determination in foodstuffs and vitamin content determinations in infant formula.
- TC 47 (Chemistry)
- TC 61 (Plastics)/SC 14 (Environmental aspects)
- TC 147(Water quality)/SC 2 (Physical, chemical and biochemical methods)
- TC 212/WG2 (IVD reference systems) (ISO 15193 and 15194 revisions)

Regional standardization bodies with work items of potential interest have been identified as:

- CEN/TC 230 (Water analysis)
- CEN/TC 460 (Food authenticity)/WG4 (NMR Analysis)] (regional standardization initiative)

Care will have to be taken in managing such interactions to ensure that the ISO mechanisms for providing input and feedback into the activities of TCs and during the development of ISO standards are respected.

### **Commercial and non-NMI CRM/PT providers and Accreditation Bodies**

The majority of testing laboratories currently use CRMs obtained from commercial suppliers and participate in EQAS/PT schemes where performance is evaluated against consensus rather than reference values. Engagement with CRM suppliers and accreditation bodies will be important to assess how the CCQM and the OAWG can work with this community to help ensure testing laboratories have access to appropriate calibrants to ensure the traceability of their measurement results. Engagement with PT service providers may allow OAWG members to better assess the needs in this sector and the areas of highest impact where the provision of reference values may have the highest impact. A potential route of engagement may involve workshops to educate chemical and clinical testing laboratories, and accreditation bodies, on the importance of accuracy-based PT programmes and issues of the metrological traceability of reference values. The issues associated with these areas are presented in Table 2.

**Table 2.** Issues in relation to commercial and non-NMI CRM/PT providers. These are organized with respect to key stakeholders, key issues, proposed way forward and the outcomes that the OAWG are seeking from these engagements.

	<b>Commercial and non-NMI CRM providers</b>	<b>PT providers</b>	<b>Accreditation Bodies</b>	<b>Standards and Guidance</b>
<b>Key Stakeholders</b>	<ul style="list-style-type: none"> <li>● Providers of pure organics/solutions that are the calibrants being used to provide traceability by testing laboratories</li> <li>● Key groups include: Sigma, Merck, LGC Standards etc.</li> <li>● Instrument manufacturers who provide calibration materials as CRMs</li> <li>● National bodies producing CRMs</li> </ul>	<ul style="list-style-type: none"> <li>● Clinical and forensic EQAS providers</li> <li>● Food safety and environmental regulatory compliance organizations</li> <li>● EPTIS database coordinators</li> <li>● Reference laboratories</li> </ul>	<ul style="list-style-type: none"> <li>● ILAC</li> <li>● Regional Accreditation bodies</li> <li>● National ABs that have engaged in this discussion, e.g. NATA, CNAS</li> </ul>	<ul style="list-style-type: none"> <li>● ISO standards – 17025, 17034, 17043, 15194</li> <li>● Future ISO REMCO Guides and Standards</li> <li>● ISO TCs developing standards incorporating organic analysis</li> </ul>
<b>Key Issues</b>	<ul style="list-style-type: none"> <li>● Some commercial providers wish to participate in CCQM comparisons to demonstrate their capabilities</li> <li>● Most of these providers are accredited, however there is no mechanism for PT participation to underpin this accreditation</li> <li>● Would PT programmes be of value and what would they need to look like to be of most value?</li> <li>● Can NMIs provide more CRMs that can be used “universally” as higher level calibrants that commercial CRM producers can utilize, e.g. NIST PS1 benzoic acid for qNMR, NMIJ qNMR assigned pesticide standards</li> </ul>	<ul style="list-style-type: none"> <li>● In areas where measurement results have critical implications there are PT schemes that are not accuracy based</li> <li>● Acknowledging that reference values cannot be provided for all measurands, can we better promote the use of reference values when these capabilities are available?</li> <li>● Can we better take on board priority areas where reference value capabilities would be most desired?</li> </ul>	<ul style="list-style-type: none"> <li>● ABs are accrediting CRM producers without an infrastructure to assess their capabilities (e.g. via PT programmes), can CCQM assist in this?</li> <li>● Why do ABs think there is not a need to have such an infrastructure?</li> <li>● Should there be a greater focus on the importance of reference values for PT schemes?</li> <li>● Acknowledging that not all PT programmes can have a reference value, where are they most important and what can CCQM do to assist?</li> </ul>	<ul style="list-style-type: none"> <li>● Consistent terminology and suitable practical guidance for usage</li> <li>● Requirements consistent with role of “primary calibrator” in establishing SI traceability</li> <li>● Guidance is available on what is a CRM and their appropriate use, but this remains an issue with the user community</li> </ul>

<b>Way Forward</b>	<ul style="list-style-type: none"> <li>● Workshop with accreditation bodies and CRM providers to discuss the issue and what would be of value</li> <li>● BERM meetings may provide a forum for these discussions</li> <li>● CCQM considers investigation of priorities for CRMs for use as higher order calibrants by commercial producers</li> </ul>	<ul style="list-style-type: none"> <li>● Possible workshop with PT providers to promote the value of reference values. Would this aim to cover a breadth of sectors or should it be targeted?</li> <li>● CCQM considers how NMIs can provide reference values for PTs more effectively</li> </ul>	<ul style="list-style-type: none"> <li>● CCQM, accreditation bodies, CRM producers and ISO REMCO consider joint seminars on CRMs, similar to format used by JCTLM</li> <li>● NMIs provide greater input into third-party accreditation of CRM producers</li> </ul>	<ul style="list-style-type: none"> <li>● Maintain existing liaison with ISO-REMCO and JCTLM</li> <li>● Establish mechanisms to provide feedback or liaison as appropriate with relevant ISO TCs</li> <li>● Input into development of standards for pure material and calibration solution CRM preparation and assignment</li> </ul>
<b>Outcomes</b>	<ul style="list-style-type: none"> <li>● Improved international demonstration of the comparability of traceable calibrants that are widely used from commercial CRM providers.</li> </ul>	<ul style="list-style-type: none"> <li>● Improved assessment of the accuracy of testing laboratory results via the increased utilization of accuracy-based PT</li> <li>● Better feedback of where reference values for PT add most value</li> </ul>	<ul style="list-style-type: none"> <li>● Improved international demonstration of the comparability of traceable calibrants that are widely used from commercial CRM providers.</li> </ul>	<ul style="list-style-type: none"> <li>● Consistent description of (C)RM/calibrator requirements for organic analysis in ISO standards</li> <li>● Harmonized guidance for</li> <li>● Improved guidance on use of CRMs and appropriate use of PT materials</li> </ul>

The WG has prioritized interactions with CRM producers and PT providers as its highest priority area. Effective interactions between this community and the CCQM community will lead to the best outcomes for users of these services and ensure a more robust pathway towards traceable and accurate measurements. As this topic is a cross-WG issue it will be progressed in conjunction with the broader CCQM. The second highest area of prioritization is interactions with the laboratory medicine community. This will focus on better utilizing the existing linkages WG members have with these communities and being more proactive in information sharing between the OAWG and IFCC, JCTLM and other key clinical groups. Other areas that have been flagged as potential stakeholder groups where we should endeavor to establish a stronger liaison are national and regional reference laboratories and the broader research community.

### 5.3. PROMOTING GLOBAL COMPARABILITY

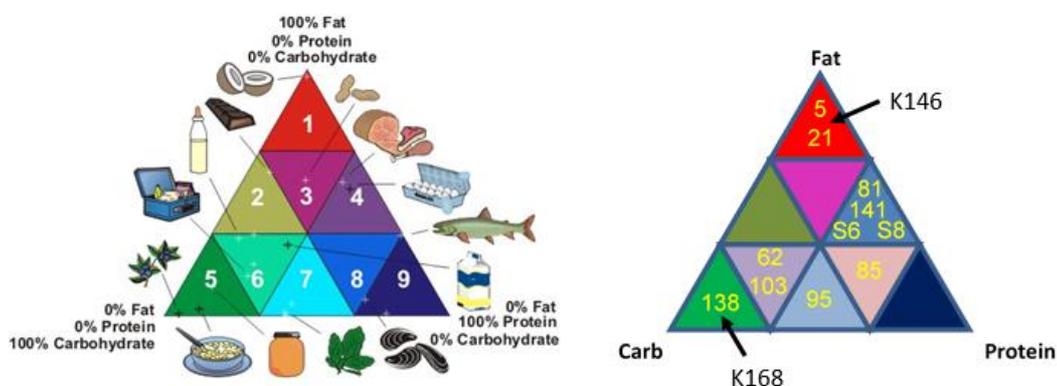
As at October 2020, 61 key comparisons were entered into the KCDB under the scope of the terms of reference of the OAWG. These were co-ordinated by the OAWG itself or by the relevant RMO technical committee. The breakdown of comparisons across the different sectors is shown in Table 3. Seventeen new key comparisons were finalized over the period 2017-2020. The specific details of the key comparisons co-ordinated by the OAWG during this period are discussed in Annex 1 Section 3.3.

**Table 3.** OAWG Key comparisons for different areas (as of 5 Oct 2020)

Area of measurement	Number of Key Comparisons		
	2012	2016	2020
Organic purity	3	5	6
Calibration solutions	4	4	9
Food matrix	6	10	12
Environmental matrix	2	5	5
Clinical matrix	9	14	18
Forensic (all ethanol)	4	5	9
Anti-doping	1	1	1
Advanced material	0	0	1
TOTAL	29	44	61

The largest number of comparisons carried out have been in the food and clinical sectors and were aimed at underpinning these two priority areas as flagged by the OAWG members in 2016. The OAWG strategy for the coordination of Track A key comparisons is summarized in Annex A section 3.1 and assesses the different measurement challenges across different sectors. As an example, for the food sector the AOAC food triangle was considered as a basis for examining different types of challenges with respect to the properties of food types. The key comparisons carried out to date across the triangle are shown in Figure 5.

**Figure 5.** AOAC food triangle and location of OAWG key comparisons across sectors

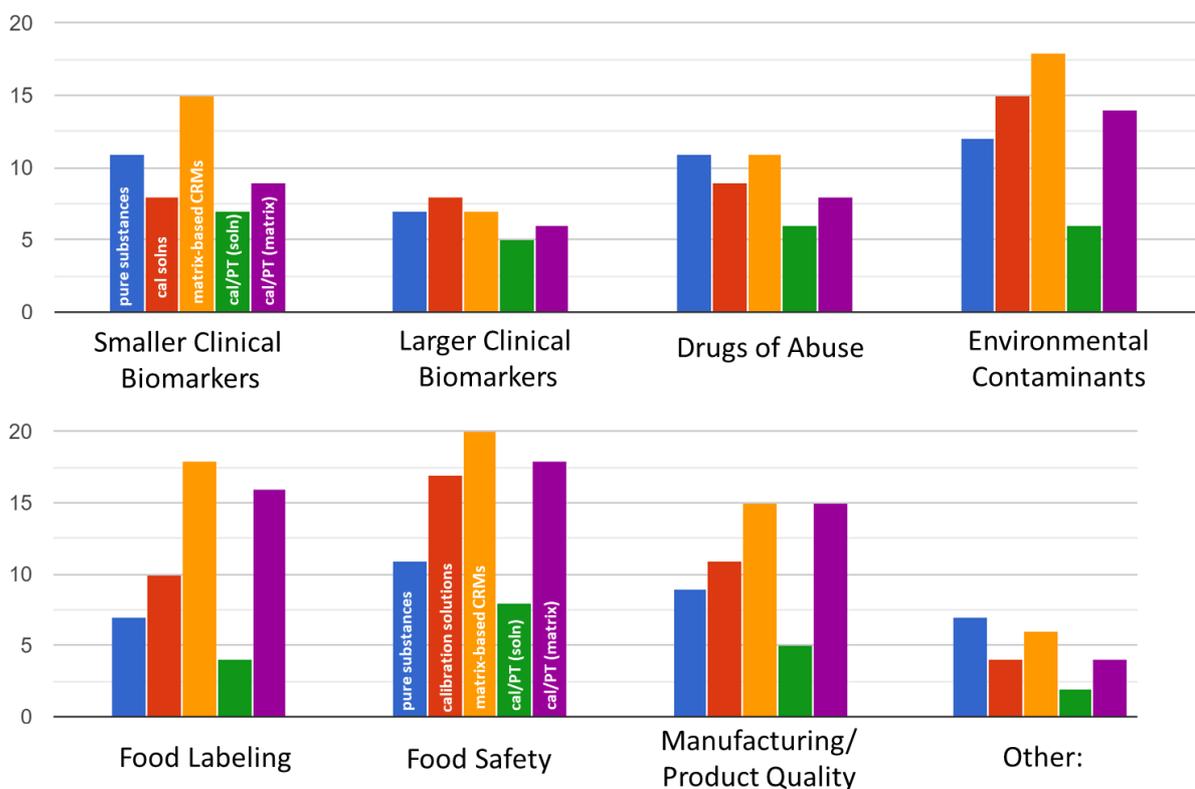


To assess the strategic priorities for the period 2021-2030 an OAWG survey was co-ordinated in March 2020. The survey assessed members' priorities and feedback across a range of issues on the infrastructure related to the promotion of global comparability. One part of the survey asked members to rank their institute's interest in each type of comparison:

1. Core Key Comparison (Track A) – Pure substances
2. Core Key Comparison (Track A) – Calibration solutions
3. Core Key Comparison (Track A) – Matrix materials
4. Model 2 Comparison - Certified Reference Materials or PT samples
5. Specialized Key Comparison (Track C)
6. Pilot study (Track D)

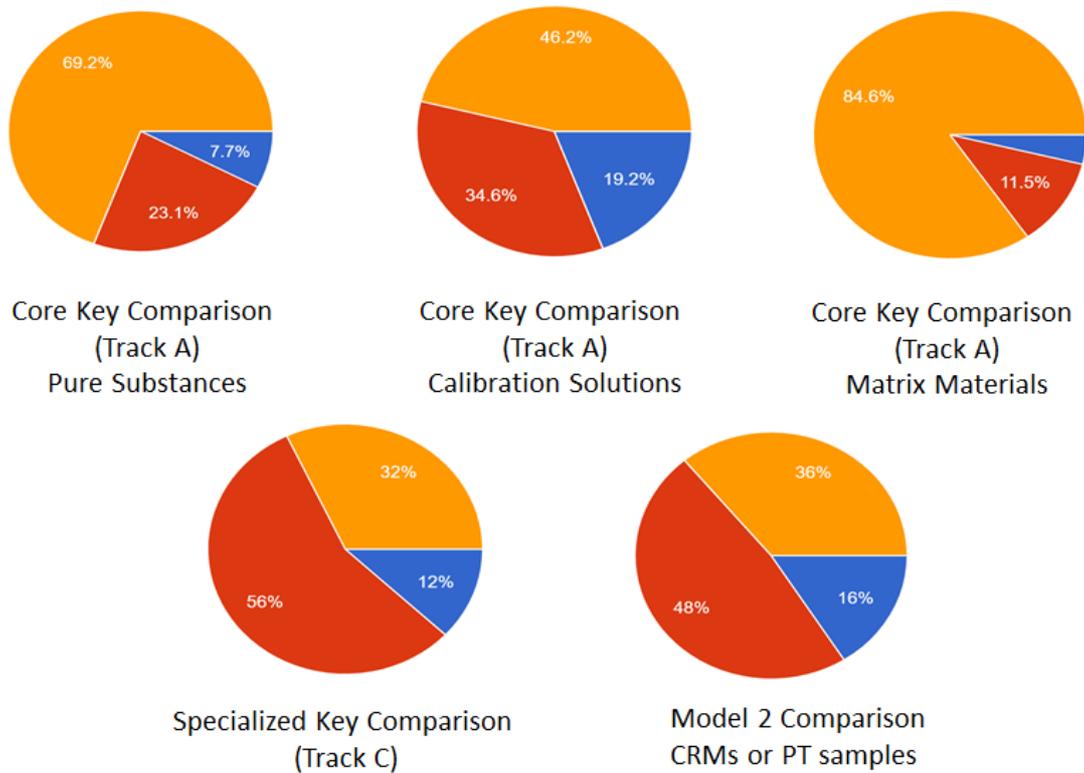
The feedback is presented in Figure 6 below.

**Figure 6.** Priority services for OAWG members across sectors. Services include: (■) pure organic calibration materials, (■) solution calibration materials, (■) matrix-based reference materials, (■) calibration/PT services for chemical purity and calibration solutions, and (■) calibration/PT services for matrix-based measurements.

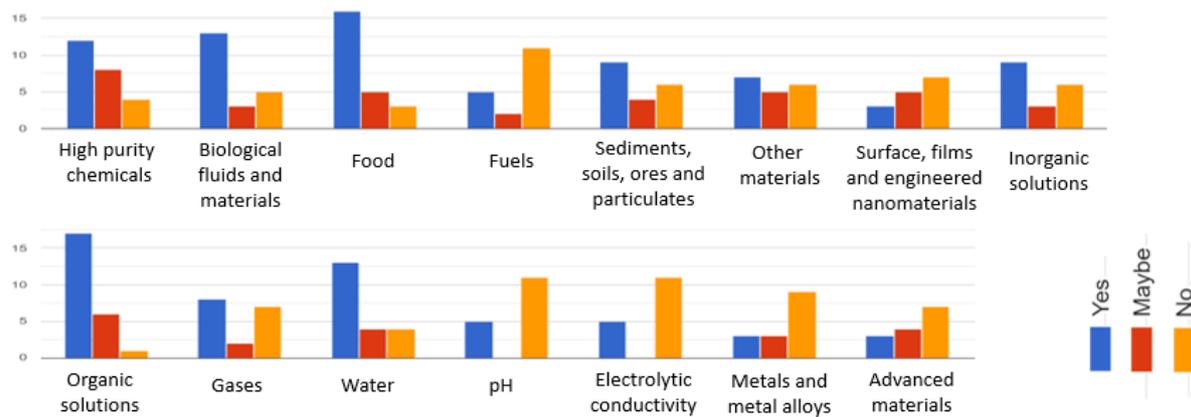


For the purpose of the survey, demonstrative examples were provided to help in the selection of responses for their priority services across the various OAWG-interest sectors. For smaller clinical biomarkers these included hormones and immunosuppressants. Larger clinical biomarkers included peptides and measurands associated with “omics” applications. Drugs of abuse of interest were noted to range from steroid metabolites to illicit drugs, including cannabis. Food labeling typically includes the quantification of vitamins and nutrients in foods and supplements, and methods for assuring provenance and for fraud detection. Food safety is more focused on specific, regulated contaminants in foodstuffs, such as mycotoxins in grains, or contaminants or leachates from food contact materials. Manufacturing and product quality considered examples such as contaminants in cosmetics and medicines, alcoholic beverages and phthalates in plastics. The ‘other’ sector included antibiotics and veterinary drugs, food additives, cannabinoids in illicit drugs and recreational/therapeutic products, organometallic compounds, pharmaceuticals, aqueous ethanol, pure organic calibration materials for qNMR, VOCs, siloxanes and dairy products.

**Figure 7.** Prioritization of comparison types across services: (■) High (critical for demonstration of capabilities, CMCs), (■) Medium (useful for demonstrating and/or building capabilities), and (■) Low (of little importance or impact).



**Figure 8.** Survey feedback from OAWG members on institutes' intentions to submit and/or maintain single measurand CMCs (i.e. individual CMCs and not broad scope CMCs).



**Table 4.** Specific priority areas and/or competencies that need to be demonstrated in these comparisons from OAWG member priorities assessed in March 2020 survey

<b>Service Area</b>	<b>Competencies (Class and Types)</b>
Organic pure substances	<p><i>Classes:</i> mycotoxins, sugars, drugs of abuse, cannabinoids, pharmaceuticals, small and medium sized clinical analytes, peptides, low purity plant isolate materials, PBDEs, pesticides, PAHs, preservatives, toxins</p> <p><i>Types:</i> salt materials, ultra-pure materials, SVOCs, pure organic calibration materials for qNMR</p>
Calibration solutions	<p><i>Classes:</i> cannabinoids and illicit drugs, small clinical biomarkers, biological macromolecules such as ribo- and deoxyribo-nucleotides, sugars, mycotoxins and other toxins for food and water safety, pesticides and environmental contaminants, SVOCs in organic solution, aqueous ethanol</p> <p><i>Types:</i> comparisons with broad scope applicability that demonstrate the maximum types of OAWG competency areas</p>
Matrix materials	<p><i>Classes:</i> clinical biomarkers and drugs of abuse (in urine, serum and plasma), contaminants, residues and additives (antibiotics, pesticides, mycotoxins, acrylamide) in foodstuffs (vegetables, fruits, maize, cereals, breads, meat, milk), vitamins and nutritional content in foodstuffs (meat, milk and other foods), environmental contaminants (antibiotics, hormones, pharmaceuticals) in water, and cannabinoids in illicit, recreational and therapeutic products</p> <p><i>Types:</i> comparisons with more analytes and commutable matrices, and with measurands and HDTLS statements intended to support broad claims</p>

**Table 5.** Priority areas proposed for Track C comparisons from OAWG member priorities assessed in March 2020 survey

<b>Type</b>	<b>Area Proposed</b>
Track C	<ul style="list-style-type: none"> <li>● Pure organics that are salt materials or without chromophores</li> <li>● Mycotoxins (and other toxins)</li> <li>● Newer pesticides in food/vegetables</li> <li>● Antibiotics in food</li> <li>● Marine biotoxins in seafood</li> <li>● Process contaminants in foods (e.g. acrylamide), food safety (e.g. fluoronitrile in egg powder)</li> <li>● Steroid hormones such as estradiol present at low mass fraction levels, and clinical materials (procalcitonin in serum, pure antibody, antibodies in serum)</li> <li>● Vitamins and pharmaceutical drugs in biological matrices</li> <li>● Emerging environmental contaminants</li> <li>● PFAS in environmental matrices and biota</li> <li>● Hormones in water</li> <li>● Cannabis (potency, and residues - solvents, pesticides and mycotoxins)</li> <li>● Additives in plastics, e.g. Bisphenols in plastics</li> <li>● Microplastics and polymers</li> <li>● Low/high polarity organic contaminants with low/high MW in fuel oil</li> </ul>

The survey results and VCs held during 2020 to investigate OAWG member priorities have fed into the planning of our suite of comparisons for the 2021-2030 period. This overlays with our planned frequency for the four types of comparisons in the OAWG:

- Track A; 1-2 comparisons per year
- Model 2; as identified, driven by strategic need
- Track C; at most 1 comparison per year, driver is strategic need
- Track D; as required, driver is research and development need

**Table 6.** Proposed Core Key Comparisons (Track A) OAWG priority areas for 2021 to 2030, including comparisons from previous strategic plan period of 2017-2020

Year	Core Key Comparisons (Track A) Pure Materials and Calibration Solutions	Core Key Comparisons (Track A) Matrix Materials
2017	<b>CCQM-K78.a: Multi-component aqueous solution</b> [Aqueous Calibration; Mass > mg/kg; P]	<b>CCQM-K141: Polar analyte in high protein food</b> [Food: Mixed; Mass > mg/kg; P]
2018	<b>CCQM-K148.a: Non-polar pure organic</b> [Purity; MW 100-500; NP]	<b>CCQM-K146: Non-polar analyte in high fat food</b> [Food: High fat; Mass > mg/kg; NP]
2019		<b>CCQM-K159: Biomarkers in clinical matrix</b> [Clinical: Serum; Mass > µg/kg; P/NP]
2020		<b>CCQM-K168: Analyte in high carbohydrate food</b> [Food: Carbohydrate; Mass > µg/kg; NP]
2021	<b>CCQM-K78.b: Multi-component organic standard solution</b> [Organic; Mass fraction > µg/kg; NP]	
2022	<b>CCQM-K148.b: Polar pure organic</b> [Purity; MW 75-500; P]	<b>Polar analyte in high protein food</b>
2023		<b>Analyte in abiotic matrix (soil/sludge)</b>
2024	<b>CCQM-K148.c: Large MW pure organic</b> [Purity; MW 500-1000, P or NP]	<b>Analyte in clinical matrix</b>
2025	<b>CCQM-K78.a.1*: Multi-component aqueous solution</b> [Aqueous; Mass fraction > µg/kg; P]	<b>Analyte in mixed composition food</b>
2026	<b>CCQM-K148.a.1*: Non-polar pure organic</b> [Purity; MW 75-500; NP]	<b>Non-polar analyte in food</b>
2027		<b>High MW analyte in clinical matrix</b>
2028	<b>CCQM-K78.b.1*: Multi-component organic standard solution</b> [Organic Calibration; Mass fraction > µg/kg; NP]	<b>Analyte in abiotic matrix</b>
2029		<b>Polar analyte in high protein food</b>
2030	<b>CCQM-K148.b.1*: Polar pure organic</b> [Purity; MW 75-500; P]	<b>Analyte in clinical matrix</b>

\* Track A Pure Materials and Calibration solutions from 2025 onwards will be identified using currently unassigned number series. K148.a.1, K78.a.1, etc. are used for information purposes only to indicate correspondence with currently assigned comparisons.

The series of Track A key comparisons proposed in Table 6 aim to cover the priority areas for demonstration of capabilities within the WG that are required to support the current and planned work programmes of the majority of members. The selection of each model system will be carefully considered to attempt to gain maximum value from each study, while also ensuring that the chosen measurands are appropriate for the broader WG. Current suggestions for the model systems for the next four years are:

#### 2022 Polar analyte in high protein food

- Veterinary drugs in meat, antibiotics in milk or meat, sulfonamides in fish, prawn or muscle
- The combination of polar and non-polar analytes has been suggested to maximize the value and this type of approach will be considered for each KC

#### 2023 Analyte in abiotic matrix (e.g. soil/sludge)

- PAHs in marine sediment, PFAS in sludge, PCBs in biota
- Similarly it was suggested that this could be combined with a polar analyte if an appropriate environmental matrix material was available

#### 2024 Analyte in clinical matrix

- Triglycerides in serum and tacrolimus or sirolimus in whole blood were suggested, but the measurand will be chosen in liaison with IFCC in order to align with their needs if possible
- It was suggested that a higher-level analyte could make up the Track A component and then a lower concentration clinical analyte be considered as a parallel Track C comparison

For more specialized capabilities the series of OAWG Track C key comparisons will continue with the feedback summarized in Table 5 taken into consideration in our planning. As the international environment changes, evolving priorities in relation to global measurement challenges will also be taken into account to ensure the WG is addressing current needs.

There are a number of areas of capability demonstration that the WG did not cover in its last strategic plan and three of these have been flagged as occurring as upcoming RMO comparisons. The area of volatile analytes in solution will be covered by a SIM regional comparison for BTEX solutions in 2021. All WG members with capabilities in this area should participate. UME recently co-ordinated a PFAS in ground water Track C comparison for WG members, however the general issue of the quantification of analytes present at low level in water is an important one. This will be further covered by a EURMET comparison for estrogens in water in 2022. This is a very topical selection of measurand and as the WG is unlikely to have a specific Track A comparison for aqueous matrices this will provide an opportunity for WG members that need to benchmark these capabilities. Many WG members have highlighted the measurement of traditional contaminants, such as pesticides, in food (particularly fruit and vegetables) as a continuing core capability that is required to be demonstrated. An AFRIMETS comparison for pesticides in fruit planned for 2021 will provide an excellent opportunity for the experienced NMIs/DIs for whom the provision of services in this area is a major focus. More importantly it will allow developing economies to participate in a comparison involving a less technically challenging measurand than the likely choices for the Track A food comparisons. AFRIMETS are also planning to coordinate a mycotoxins in nuts comparison in 2022, which may offer WG members the chance to demonstrate capabilities for this highly important class of analytes in an area of the food triangle that has not been covered to date by comparisons undertaken at the OAWG level. The planning for OAWG comparisons will aim to take into account RMO activities so as to allow for the widest coverage of comparison needs as mapped against capabilities.

### **Evolution of Broad Scope CMCs**

The introduction of broad scope CMCs has arisen in response to the increasingly large number of individual CMCs listed in the KCDB database. It is unsustainable for RMOs and the KCWG to review new CMC claims in addition to undertaking a 5-year re-review of all existing CMC claims. As of 2020, the KCDB

maintains about 1521 organic CMCs. In the past 4 years, the largest decrease in the number of specific CMCs were in Categories 3 and 13. The decrease in Category 3 CMCs coincided with their review in Cycle XXI, where a number were deleted after the approval of a smaller number of broad scope CMCs. This resulted in a decrease in CMCs in this area by about 8%.

The full range of organic CMCs were supported by 61 OAWG key comparisons, an increase in the total number of key comparisons by 17 in the past four years.

**Table 7.** Current (as at 5 Oct 2020) and past (2012, 2016) CMC status

Category	Number of CMCs			% Increase (2020 relative to 2016)
	2012	2016	2020	
1. High purity organics	327	476	463	-3
3. Organic Solutions	473	491	321	-35
5. Water	8	10	29	+190
9. Advanced materials	12	10	23	+130
10. Biological fluids and materials	179	200	229	+15
11. Food	157	142	278	+96
12. Fuels	2	6	9	+50
13. Sediments, soils, ores and particulates	322	314	168	-46
14. Other materials	1	1	1	0
<b>TOTAL</b>	<b>1481</b>	<b>1650</b>	<b>1521</b>	<b>-8</b>

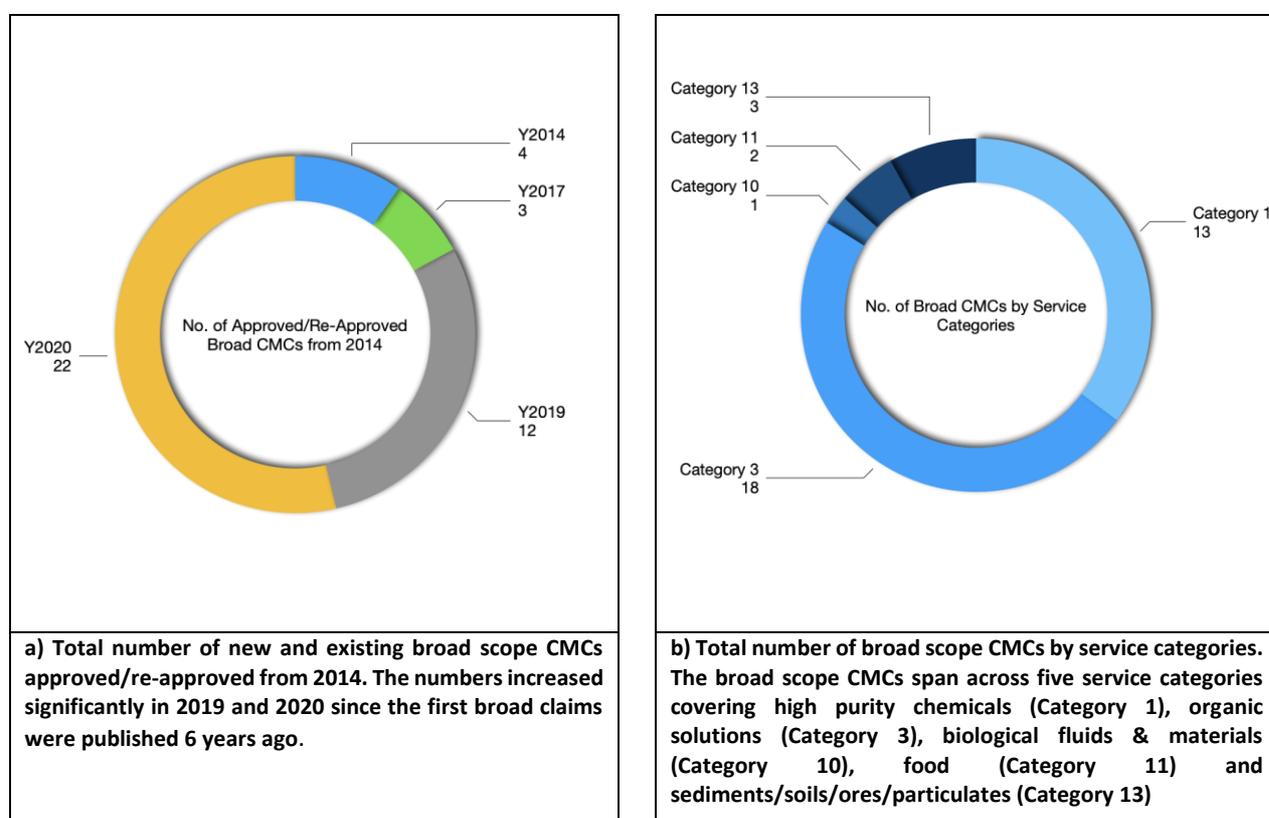
The recommendations from the 2016 CIPM Working Group on the Implementation and Operation of the CIPM MRA promoted the concept of broad scope CMCs. It also proposed that NMIs/DIs consider the percentage coverage of their measurement services by CMCs as the best metric of success, rather than the total number of CMCs. The OAWG had begun drafting a set of criteria to outline the expected evidence that would be required to underpin broad scope CMCs. These proposed differing levels of evidence required to support three classifications of broad claims corresponding to varying degrees of structural, polarity and/or molar mass diversity:

- Classification 1.** Homologues with identical functional groups and common classes with well-defined range of structural variation (in same matrix type if applicable)
- Classification 2.** Classes of analytes with greater structural diversity (in same matrix type if applicable)
- Classification 3.** Broad scope claim covering entire or major subset of the HFTLS statement

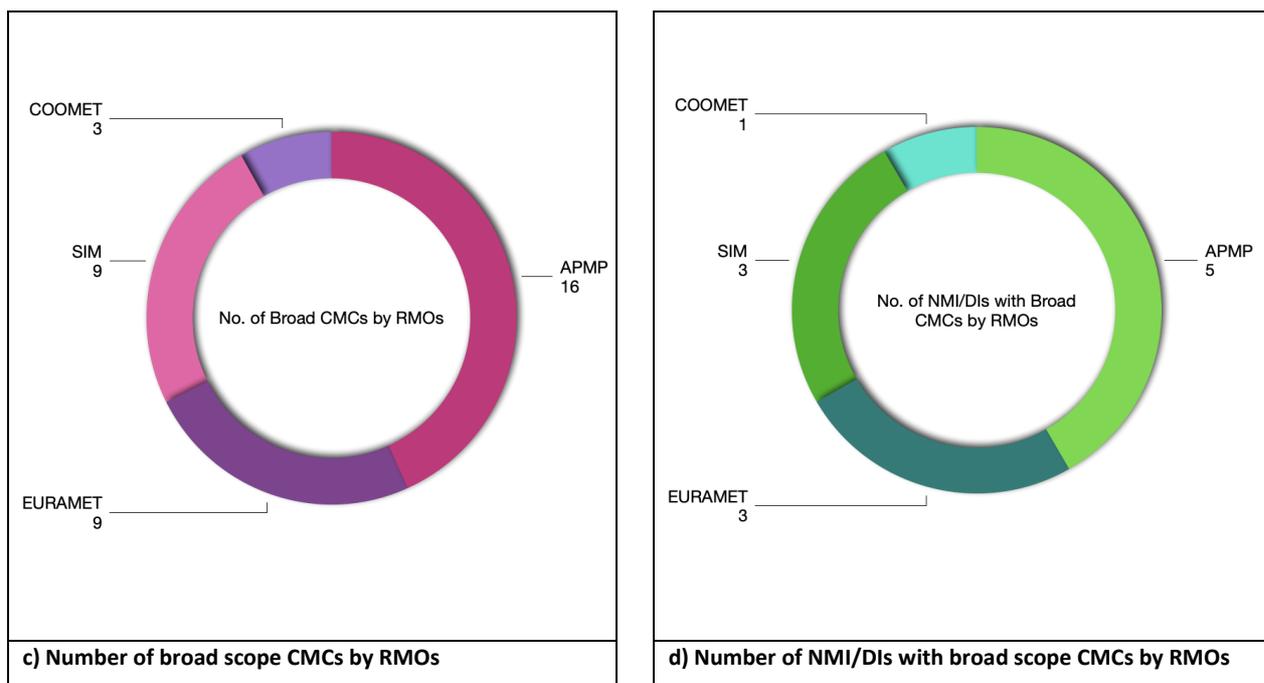
The first formal written guidance was made available in April 2018 and in the same year, six NMI/DIs implemented the guidelines in the CMC Cycle XX. Out of 20 new broad scope CMCs submitted, 10 (50%) were approved. The majority covered Category 1 services while the rest covered Categories 3 and 10 services. The guidance document has been continuously improved to better address the needs of the WG members. In CMC Cycle XXI, the OAWG saw up to 32 additional broad scope CMCs submitted, with a higher success rate. 21 (66%) of the claims are being fast-tracked as institutes followed the guidelines more carefully when providing evidence to support their broad scope CMCs. 15 (71%) of broad scope CMCs covered Category 3 services, with the rest corresponding to services in Categories 5 and 11.

Notably, some of the broad scope CMCs overlapped with existing specific CMCs of the NMI/DIs. Several NMI/DIs deleted specific CMCs that were now covered within their broad scope ones. However, others have chosen to maintain the co-existence of broad scope and specific CMCs in some cases. The need for specific descriptions of their services in order to meet the needs of certain stakeholders was the stated justification. This raised concerns that the proliferation of claims could defeat the original purpose of broad scope CMCs. At the April 2020 meeting of the KCWG it was agreed that alongside the submission of broad scope CMCs, specific CMCs which overlap should be reviewed and submitted with appropriate justifications for their co-existence. An example of this that was cited was aqueous ethanol CMCs produced to underpin national drink driving legislation where it may be appropriate to have this specifically identified as a CMC entry. The issue of overlapping CMCs will require future attention and further discussions, as the broadening of CMC scope may not only impact an individual NMI/DI, but also others within the same economy.

**Figure 9.** Number of broad scope CMCs<sup>16</sup> according to a) Year, b) Service Category, and c) RMO. The number of NMI/DIs within specific RMOs with broad scope CMCs is illustrated in d).



<sup>16</sup> The CMC data is correct as at 29 Sep 2020



### Managing Sub-Optimal Track A KC Performance and Exceptional Circumstances

The OAWG Strategy Document for 2017-2026 highlighted the challenge in dealing with situations where an NMI/DI with existing broad scope CMC performed sub-optimally in a Track A KC with closely related capabilities. The guidance document now provides recommendations on the expected actions to be taken in such situations. In a real example, an NMI with an existing broad scope CMC on purity performed root-cause analysis and underwent a round of peer review covering the actions taken after a sub-optimal performance in a Track A purity comparison. The exercise allowed their existing broad scope CMCs to be re-approved following a re-review process by the KCWG. In another example, the Track A KC CCQM-K146, which covered low polarity analytes in high fat food: benzo[a]pyrene in olive oil was concluded with a handful of NMI having poor performance and desiring to repeat the study. Another batch of comparison material was rapidly made available by the coordinating institute. This allowed the concerned institutes to demonstrate their competencies in the subsequent KC CCQM-K146.1 in a timely manner. In view of the potential impact of a sub-optimal KC performance on a KCDB-listed broad scope CMC, the OAWG will reinforce the need for prompt corrective actions, or otherwise the associated broad scope CMC will risk being greyed-out within or deleted from the KCDB.

It is expected that the OAWG will continue to discuss the point at which ongoing sub-optimal performance in a KC cannot be admitted to support a broad scope CMC, e.g. even if the uncertainties are significantly enlarged to cover the deviation from the KCRV or if only in-house re-validation of methods are undertaken.

The criteria for acceptance of CMCs are detailed within CIPM MRA-D-04 Guidance Document *Calibration and Measurement Capabilities in the context of the CIPM MRA*. It is clearly stated and is common knowledge that the results of key and supplementary comparisons are the ideal supporting evidence for CMC acceptance. However, evidence from alternative sources can be leveraged to underpin CMCs for which comparison results are not yet available. This includes: 1) documented results of past CC, RMO or other comparisons (including bilaterals), 2) knowledge of technical activities by other NMIs, including publications, 3) on-site peer-assessment reports, 4) active participation in RMO projects and 5) other available (and documented) knowledge and experience. In the unfortunate case of a shut-down of an institute for either economic or fiscal reasons or more recently in the case of the COVID-19 pandemic, there will need to be consideration of utilization of these sources as stop-gap evidence in lieu of results

of a current Track A key comparison. It should be incumbent on the affected institute to submit evidence that clearly articulates: 1) the exceptional reasons why participation was not possible and 2) a list of acceptable supporting evidence that demonstrates the good standing of their relevant measurement services.

### **Areas for Improvements and OAWG's Strategies**

*Design and Implementation of KCs to Promote Broad Claim Submissions.* It is recognized that very broad Classification 3 CMCs would normally be submitted by NMI/DIs who have either the means to participate in many comparisons, or who already have extensive KC participation and therefore the proven experience to make such claims. These NMI/DIs comprise a small subset of the OAWG. Hence, encouraging an initial focus on the submission of Classification 1 and 2 broad scope CMCs would potentially generate more uptake, particularly among the smaller and specialized institutes.

The design of KCs such that they can accommodate both existing broad scope CMCs and the intentions from NMI/DIs wishing to apply for them will become increasingly critical. Given that there are limited opportunities to participate in KCs each year, and that participation typically requires a considerable investment of manpower and resources, potential KCs should be evaluated in terms of the types of Classification 1 and Classification 2 broad scope CMCs these would potentially support. Evaluations could be discussed with OAWG members as part of the study proposal process, and this would assist the WG in selecting studies which fit the needs of its members. While this is similar to what is being practiced now, having an explicit discussion surrounding broad scope claims may assist NMI/DIs in viewing comparison participation with respect to their broader recognition goals, and ultimately encourage broad scope CMCs instead of the proliferation of specific CMCs.

Additionally, NMI/DIs which have common broad scope CMC aspirations should consider using (and/or be encouraged to use) Track C comparisons to collectively accelerate the process. That is, performance in a previous Track A comparison could be used together with that achieved in a Track C comparison intended to demonstrate the ability to submit Classification 1 or Classification 2 broad scope CMCs.

It should be encouraged that comparisons (particularly Track A) include analytes covering at least two classes, if not covering more than one region of the analytical space. For instance, selecting as analytes pesticides from different classes would be more useful than a comparison using multiple pesticides from the same structural class. This may not always be possible or practical. Participation in relevant Track A comparisons is required for all broad scope claims and their scope should be critically evaluated and made as wide as possible. Otherwise it may limit the ability of NMI/DIs to submit broad scope claims for years as individual NMIs may not have the resources, even if additional Track C comparisons are available, to participate in the breadth of comparisons required to underpin their specific broad claim CMCs.

The KCWG may consider providing comment and/or endorsement on the ability to use proposed comparisons in conjunction with predefined previous comparisons to facilitate Classification 1 or 2 broad CMCs. This would provide assurance to participating NMI/DIs that acceptable performance in the relevant comparisons may be sufficient to support a broad scope claim. This would also assist in identifying upfront, relevant existing broad claims which may need to be reviewed once the KCRV is known and NMI/DI performances are evaluated.

*Guidance Document Criteria.* While 12 (39%) of 31 NMI/DIs who participate in the OAWG have successfully published at least one broad scope CMC to date, some institutes still faced challenges in applying the criteria described in the guidance document for the submission of broad scope CMC. Near-term strategies have been discussed to assist NMI/DIs in the interpretation of the guidance document with the addition of examples or case studies. In the 2020 survey conducted by the OAWG, several institutes indicated that a repeating combination of analyte/component and matrix that would be valuable to them in order to support their anticipated CMC claims over the next 10 years. For example, comparisons of the quantification of PAHs, pesticides and PCBs in food/plant matrices or sediment/soils. With the aim of better defining what a broad CMC claim is and how confidence in such claims can be better demonstrated,

the guidance document will use such examples in explaining how the actual services of the institutes and existing KCs should be collectively considered in the crafting of a Classification 1, 2 or 3 broad scope CMC.

Presently, the OAWG acknowledges that broad scope CMCs of different extent are currently listed within the KCDB. As NMI/DIs continue to apply the criteria in the guidance document, the OAWG members would be able to accumulate more experience and work towards refining and harmonizing the way a broad CMC should be scoped.

*Transparency and Dissemination of the CMC Review Process.* The OAWG has held continuous discussions to assist NMI/DIs in setting and gaining better understanding on the requirements for broad scope CMC applications since April 2018. Even then, we acknowledge the need to reinforce efforts on these, both for the NMI/DIs and the CMC reviewers.

It should be reinforced that each submitted broad scope CMC should support actual services and in turn be supported by competencies demonstrated in recent KCs testing core capabilities and separately by technical peer reviews. A Task Force has been formed to create templates aimed at guiding NMI/DIs and CMC reviewers in providing or assessing the necessary evidence for broad scope CMCs. Given the complexity within the organic analysis measurement space with respect to analyte structure, polarity, stability and the makeup of the matrix, the criteria are expectedly different and dedicated templates will be made available for various categories of CMCs. Similar to the guidance document, the templates will be continuously reviewed and improved to meet the needs of the NMI/DIs and CMC reviewers.

While the concept of broad CMCs was supported by the CCQM, the OAWG acknowledges the on-going need for discussions on how to deliver a more “customer-oriented” database. This topic is a work-in-progress and the OAWG will consider options as the members become increasingly familiar with the functions and features of the new database KCDB 2.0.

*Management of Broad Scope CMC Expansion.* Maintaining broad scope CMCs in the database requires regular participation in KCs. As at 29 Sep 2020, there are close to 40 broad scope CMCs, which makes it relatively manageable for the OAWG to monitor if an institute has recent evidence to ensure on-going credibility of the broad CMCs or if remedial actions need to be undertaken. In anticipation of an increasing number of broad scope CMCs moving forward, the OAWG recognizes that it is necessary to develop effective processes not only for the review of new broad scope CMCs, but also more importantly for the monitoring of existing ones. For long term sustainability of such monitoring, the OAWG will consider strategies to guide or even stimulate institutes in making conscientious efforts to voluntarily update their competencies or take the necessary actions as soon as new evidence is available.

#### **5.4. INTERACTION WITH RMO ACTIVITIES**

The OAWG survey highlighted the following priority areas for interactions with RMOs.

- Small organic clinical markers, purity assessment of small organic compounds and organic calibration solution (APMP and AFRIMETS highlighted that members of their RMOs are still developing competencies in the value assignment of organic calibrators and are yet to participate in relevant comparisons).
- Challenges around food safety that are region specific are of key importance and merit a close relationship between the working group and RMOs. AFRIMETS flagged that members are developing capabilities related to reference measurements in food.
- Aqueous ethanol, small biomarkers in biological matrix, biofuels and food safety were all highlighted as priority areas across RMOs.
- Participation in comparisons related to EMPiR (European Metrology Programme for Innovation and Research) and European Partnership in Metrology projects.
- Input into available capacity building opportunities.
- CMC submission and review process, particularly as we transition to the KCDB 2.0 platform and as we evolve increasingly towards broad scope CMCs.

Feedback from the RMOs on their planned programmes of relevance to the OAWG is described below.

### **APMP**

Many of the activities for APMP are accomplished through engagement of various Focus Groups. Three of these are relevant to the OAWG activities: Clean Water Focus Group (CWFG), Food Safety Focus Group (FSFG) and Climate Change and Clean Air Focus Group (CCCA FG). The last face-to-face CWFG Workshop was held in November 2019 with participants from APMP Members sharing the established capabilities and challenges of their metrology institutes in related measurement sciences. The work plan for CWFG includes a MEDEA (Metrology-Enabling Developing Economies in Asia) training project. The FSFG also held a workshop in November 2019 featuring food safety related activities by participating APMP member institutes including NMIA (Australia), NIM (China), NMIJ (Japan), KRISS (South Korea), NIMT (Thailand), HSA (Singapore), and NMISA (South Africa). The CCCA FG Annual Workshop was held jointly with APMP Gas Analysis Workshop in Yogyakarta, Indonesia in August 2019, with about 100 participants including more than 50 from local or regional stakeholders. Both workshop programmes were aligned with needs and issues identified by the survey in order to provide technical education and training in TCQM, TCT, and TCFE.

Notably within APMP, the majority of pilot studies are associated with the food and biological material measurement sectors, indicating that in recent years these have become priority areas in the region. At present, the number of approved CMCs from the APMP TCQM is 2,394 in the QM area and the number of CMCs in the food sector has increased significantly. The other main area of relevance to the OAWG is high purity chemicals (17 % of total).

*Joint Collaborations between APMP and APAC.* In November 2013, the APMP-APAC Joint Proficiency Testing Working Group (PTWG) was established. Joint PTs are aimed at enhancing the metrological capability and technical competence of field analytical laboratories in the Asia-Pacific region with metrologically traceable reference values provided by NMIs/DIs to be the basis for performance evaluation. Organic analytes are definite priorities for this group.

### **AFRIMETS**

The AFRIMETS strategy is currently focused on food safety testing and capacity building through training, relevant reference material production and proficiency testing initiatives. These projects aim to establish capabilities in support of the Africa Continental Free Trade Area (AfCFTA) goals. In this vein, an AFRIMETS project funded through the PTB will see NMIs within Africa (INRAP, KEBS, NIS, NMIE and NMISA) collaborate on the value assignment of a cassava reference material for assignment of hydrocyanic acid and priority food contaminants (heavy metals, mycotoxins and pesticides) as defined through the African Union, and the Africa CODEX Standards Committee. Activities will continue to align with CODEX Alimentarius food safety regulations, the African Union Commission (AUC) studies, African Organization for Standardization (ARSO) and Africa Codex Committee (ACC) Commodity Standards under development.

The first Africa Food Safety Workshop hosted by NMISA and the FAO-IAEA RAF 5084 Africa Food Safety Network, was held in June 2018, with a second workshop planned for June 2021, in conjunction with the AFRIMETS TCQM meetings. The main workshop objectives were:

- to find mechanisms to improve regional measurement and standards infrastructure, contributing to food safety in the region.
- to expand a regional food safety network beyond laboratories by attracting other experts in the areas of mycotoxin, veterinary drug and pesticide residues and microbiological food safety from non-profit organizations, technical institutions, government regulators, commercial testing and research institutions, professional associations, as well as the private sector.
- to strengthen capacity development for food safety testing and control in Africa

Through these stakeholder engagements, reference measurements and reference material production activities continue to be identified and prioritized for the region.

The FAO-IAEA RAF 5084 project for “Strengthening Food Contaminant Monitoring and Control Systems and Enhancing Competitiveness of Agricultural Exports using Nuclear and Isotopic Techniques” is aimed at achieving the UN sustainable development goal 02 - End hunger, achieve food security, improve nutrition and promote sustainable agriculture. Overall Objective: To enhance food safety and consumer confidence and boost regional economies through the supply of safe and competitive agricultural products.

Several NMIs in Africa are participating in this project, with participation focused on developing fit-for-purpose Africa-relevant training, reference materials and PT schemes enabling accurate food safety testing within the FAO-IAEA Africa Regional Food Safety Network (IAEA RAF5078 Phase II 2016-2019 and IAEA RAF5084 Phase III 2020-2023). This network comprises National Food Safety Monitoring laboratories representing 45 countries across the continent. These are the main stakeholders utilizing/benefiting from accurate methods of analysis, calibration CRMs, matrix CRMs and relevant PT schemes, to support critical food safety testing. NMISA has engaged with laboratories in the network to provide training on reference material production and methods of analysis for mycotoxins. PT schemes for mycotoxins and pesticides in fruit have been conducted within this network since 2018.

AFRIMETS NMIs are engaging with another key stakeholder towards achieving food safety testing capacity on the continent, namely, the AOAC Sub Saharan Africa Section (AOAC-SSA) which was established in 2018. The AOAC-SSA serves as an effective vehicle to drive the improvement of analytical competence and capabilities as well as improving the standards and performance of food testing labs in this region. This will be achieved through collaboration, training and education, analytical methods development and harmonization, the extension of the scope of Official Methods (to include indigenous foods where required) and to serve as an independent and impartial scientific advisory body.

Furthermore, in the area of organic analysis many NMIs double as Standards Bureaus. Product testing and regulations, PT schemes on proximate analysis and contaminants are still in high demand and the avenue through which (NMI) services are offered to the industry for in-house QC. PT schemes therefore remain a key area within AFRIMETS. In the East African region, support from the EU through the Standards and Market Access Program (SMAP) has a focus on ensuring the quality of agricultural exports which includes testing for verification that agricultural practices do not compromise product safety.

Within the AFRIMETS RMO NMISA coordinated the NIM China APMP Zearalenone in maize proficiency test during 2019. Participation in the PT by AFRIMETS NMIs (Kenya, Tunisia) is intended to prepare the NMIs to participate in the planned CCQM OAWG Zearalenone in maize comparison in 2020/21.

It is similarly anticipated that within AFRIMETS several more RMO (supplementary/bilateral) comparisons that link to CCQM OAWG KCs will need to be conducted in order for developing NMIs to claim CMCs for which comparisons have already been completed by long-established NMIs. These will be predominantly in the Food Sector, focusing on the production of calibration solution CRMs, matrix CRMs and reference measurements of priority food contaminants (mycotoxins, pesticides, veterinary drug residues, antibiotics) and nutrients (vitamins and elements) across the AOAC Food Triangle sectors. These are still to be prioritized within the revised AFRIMETS TCQM strategy (2021-2030).

Future comparison needs identified include:

- Follow-on AFRIMETS.QM-K27: Aqueous ethanol CRM solution assay
- Pesticides in fruit (2021/22)
- Mycotoxins in nuts, grains (maize/wheat/ barley/sorghum), milk, spices, dried fruits and black tea
- Veterinary drug residues in milk and meat
- New organic CRM solution comparisons

- Mycotoxins in acetonitrile
- Pesticides in acetonitrile
- BTEX in methanol
- VOCs in methanol, trihalomethanes
- Aromatic hydrocarbons
- Aliphatic hydrocarbons

The BIPM Safe Food and Feed Capacity Building and Knowledge Transfer Programme is a valuable support function for developing NMIs especially within AFRIMETS. KEBS, INRAP and NMISA have benefited from the mycotoxin metrology CBKT Programme (2016-2019) with several mycotoxin calibration solution CRMs being produced within AFRIMETS for the first time. As more AFRIMETS NMIs establish Organic Analysis Chemical Metrology Capabilities, having access to these fundamental metrology training services will accelerate their development and eventually their ability to support CMC claims.

### **COOMET**

Most of the COOMET members do not have the appropriate analytical tools and skills to deal with metrological tasks in the field of organic analysis. For this reason, the ability of VNIIM (as the leading NMI in the field of physical chemistry measurements in COOMET) to organize key comparisons is very much limited. Nevertheless, in the last 5 years the following pilot comparisons have been agreed and carried out:

- COOMET 691/RU/16 Determination of polychlorinated dibenzo-p-dioxins and dibenzofurans in fatty matrixes (pork fat)
- COOMET 708/RU-a/16 Purity determination for organic compounds by mass balance method. Anthracene
- COOMET 654/RU/14 Cholesterol in human serum.

Determination of the purity of organic substances is a core competence of NMIs, without which it is impossible to form calibration capabilities and to develop metrological infrastructure. This area is still a priority area of VNIIM. Over the past few years, VNIIM has focused on the development of technology for the certification of pure substances that are liquids under normal conditions (aromatic and aliphatic hydrocarbons, alcohols, carboxylic acid esters, etc.) to address pressing environmental issues. In the near (2-3 years) and distant (5-10 years) perspective they plan to develop CRMs of pure substances, solutions and matrices, with a focus on objects of interest in the medical sphere for clinical diagnostics purposes. For COOMET an extremely important task is to fully master the qNMR method and to introduce it into practice. In the long term, VNIIM envisages development of a set of high-purity organic substances - internal standards for qNMR. A specific sector of activity for COOMET is the harmonization of Sulfur and Chlorine measurements in petroleum products through the development of CRMs traceable to pure organic substances chlorobenzene and dibutylsulfide.

The communication platform for strengthening cooperation and raising awareness of COOMET NMIs-members is the annual event under the aegis of Rosstandart - exhibition and forum "Precision measurements - the basis of quality and safety". In previous years the event was focused on the tasks of ensuring the uniformity of measurements and development of legal and regulatory basis. In the future, the emphasis will be placed on demonstration and discussion of the possibilities of modern measuring equipment, analysis of new methods and technologies of precision measurements.

### **EURAMET**

EURAMET set up several coordination mechanisms to ensure that Europe's metrology infrastructure and networks develop in a way that enhances industrial innovation, competitiveness and international trade, and responds to the grand societal challenges:

Joint research projects (JRPs) under EMRP and EMPIR and the establishment of joint structures which go beyond joint research, called European Metrology Networks (EMN) in the next programme (the European Partnership in Metrology) contribute to address the EU metrological needs. In the chemistry and biology area, the activities are mainly related to societal challenges in health, climate change and environment, energy, food and nutrition and aim to underpin regulation and standardization.

CCQM comparisons are covering most of the need for all EURAMET members in the specific area. EURAMET comparisons are mainly SCs or pilot studies, to cover new and additional regional needs outside the CCQM core competencies approach. They are mainly organized in the framework of these EU programmes, and some are open to other RMOs and registered in the KCDB.

For example, the JRP 18NRM01 EDC-WFD Metrology for monitoring endocrine disrupting compounds under the Water Framework Directive aims to develop traceable measurement methods for endocrine disrupting chemicals, with a specific focus on three estrogens of the first watch list (17-beta-estradiol (17 $\beta$ E2), 17-alpha-ethinylestradiol (17 $\alpha$ EE2), and estrone (E1)). The project will develop aqueous reference material (RM) which reproduces the properties of real water samples as close as possible, i.e. including suspended particulate matter and organize an interlaboratory comparison (ILC) in 2022.

## **SIM**

SIM created in 2018 a food safety and food labelling task force and has been focusing some of its events on food analysis such as the recent SIM Workshop on Mycotoxin Metrology that took place at INTI in 2018. More recently, there have been other events and cooperation agreements led by individual NMI in this field.

Food analysis to tackle the issues of safety, labelling and authenticity are among the top priorities for most of the NMIs in SIM and the needs in this area encompass nutritional constituents, contaminants and integrity. Although SIM has been expanding its activities in knowledge transfer and cooperation in this field, there are a limited number of institutes to promote regional comparisons and there is interest from the region for the OAWG to promote comparisons to underpin these needs. The success of the collaborations that were born from these workshops and regional events has also led SIM members to increase the demand for training and exchange activities within the OAWG.

Another high priority area for the region is environmental analysis. In this case, there are not many regional events that approach the topic and there is a real need for the NMI/DIs in the region to take part in OAWG activities that underpin CMC and services such as training, workshops, collaboration projects and comparisons. Finally, a third area of interest is the determination of purity of substances and in this sense, SIM will also work on developing activities such as those already mentioned, together with the OAWG.

The regional comparison currently being planned by SIM of relevance to the OAWG is a BTEX in solution comparison that will occur in 2021. As a number of OAWG members have activities in this space this may be of interest more broadly across the OAWG.

# ANNEX

## 1. GENERAL INFORMATION

CC Name: CCQM

CC Working Group: Organic Analysis (OAWG)

Date Established: 1997

Number of Members: 32 registered institutes

Number of Participants at last meeting: 68 via VC

Periodicity between Meetings: Every six months

Date of last meeting: October 2020

CC WG Chair (Name, Institute, and years in post): Dr Lindsey Mackay, NMIA, 8 years

CC WG Vice Chair (Name, Institute, and years in post): Dr Katrice Lippa, NIST, 5 years

Number of KCs organized (from 1997 up to and including 2020): 61

Number of Pilot studies organized (from 1997 up to and including 2020): 67

Number of CMCs published in KCDB supported by CC body activities (up to and including 2020): 1521

## OAWG Terms of Reference

The primary focus of OAWG activities is the critical evaluation and benchmarking of NMI/DI capabilities for the execution of "higher order" measurement procedures for well-defined organic molecular entities for which the SI traceable amount of substance is to be determined. The group will also consider, on a selective basis, similar activities for high-priority method-dependent analyses/measures.

"Organic molecular entities" are taken to exclude gaseous compounds, organometallic compounds, and large bio-molecules.

## 2. LIST OF PLANNED KEY AND SUPPLEMENTARY COMPARISONS AND PILOT STUDIES

The BIPM posts 6-monthly updates of planned comparisons for all of the working groups on its open access area. The current plan is available here:

<https://www.bipm.org/en/committees/cc/ccqm/strategy.html>

## 3. SUMMARY OF WORK ACCOMPLISHED AND IMPACT ACHIEVED (2017-2020)

The OAWG met every 6 months during the period 2017-2019 and held over 8 VC meetings in 2020. The WG had a full programme of planned Track A and Track C comparisons during this period and also coordinated two Model 2 key comparisons to test actual services for WG members. To ensure the programme of comparisons were effectively and appropriately co-ordinated there has been a focus during this period on the documentation of processes.

The "OAWG Practices and Guidelines Document" was further updated during this period (February 2019 last version). The document outlines the four-track approach to comparisons (and other aspects of the functioning of the WG). A series of templates and checklists were prepared to aid study coordinators. This included a Comparison Coordination Checklist to assist the coordinating laboratory in the preparation of initiating, implementing and completing a key comparison. Two Word document templates for use by the coordinating laboratory to generate both the 1) study protocol and 2) draft and final reports for Key comparisons were also devised. These documents and templates are now serving as the basis for other working groups within the CCQM.

Additional technical guidance documents worked on during this period included:

- Reporting Significant Figures in Results of OAWG Comparisons

- Decision Guide for Selecting CCQM Model Key Comparison Reference Value (KCRV) Estimation Procedures

Notably, the Decision Guide for KCRV estimation has recently been followed by the launch of an *ad hoc* working group to scope and inform regarding the approaches for KCRV estimation utilized across the CCQM. All of these templates, checklists and guidance documents are available as open access in the OAWG working documents.

### 3.1 PROGRESSING METROLOGY SCIENCE

The OAWG contributed to the CCQM “Workshop on Advances in Metrology in Chemistry and Biology” in April 2019, which celebrated the 25th anniversary of CCQM. The presentation “Development of nuclear magnetic resonance as a tool of quantitative analysis for organic materials” was given by NMIJ and covered this highly important aspect of organic purity assessment. The OAWG also contributed papers for the associated *Metrologia* special edition. A paper on qNMR was prepared by a group of OAWG members and NMIA provided a paper outlining the organic purity assessment of a key steroid. A number of other papers were prepared by the WG at this time including an overview of the OAWG activities across the organic purity assessment field and an overview of high-accuracy clinical applications.

Many members of the OAWG contributed to the BIPM led IUPAC Project on Organic Purity Assessment. This resulted in a detailed report into different approaches to purity assessment and was published in 2020. The OAWG had strong linkages to the BIPM Mycotoxin Metrology Capacity Building and Knowledge Transfer Programme with the first formal Track C comparison CCQM-K154.a for trans-zearalenone in acetonitrile solution co-ordinated in conjunction with the OAWG.

The WG held a number of internal technical workshops to progress key areas:

- Measurement uncertainty estimation for matrix material assessment (October 2019)
- Purity of organic salt materials: technical seminar (October 2019)
- Issues related to best practice organic purity determination (April 2018)
- KCRV estimation approaches (September 2017)
- General measurement uncertainty approaches (September 2017)
- Measurement uncertainty estimation for pure organic purity assessment (October 2016)
- Several joint sessions with the PAWG on IDMS approaches (in relation to P164 human growth hormone in serum) and the K115 series on peptide purity assessment

At the September 2018 OAWG meeting there was a dedicated discussion on approaches to meeting the CIPM Traceability requirements. During the last four years the WG has put an increased focus on the traceability of all calibrators used by institutes in key comparisons. This has included adding to our report template a section clearly articulating these aspects and any in-house assessment involved and the evidence for demonstration of competence.

### 3.2 IMPROVING STAKEHOLDER INVOLVEMENT

The OAWG has had limited external engagement during this period due to a stronger focus on internal workshops covering technical issues. Two examples of external engagement are:

- In September 2016 many OAWG members participated in the BIPM/WADA workshop and presented work from their institutes related to this field. Lindsey Mackay presented on CCQM key comparisons and EQAS. Stronger ties with WADA were developed for several OAWG members following the workshop and WADA has continued to prioritize needs for reference materials within its field.
- In April 2018 the WG held a technical workshop on best practice organic purity determination. One of the key speakers was from EDQM and it was highly valuable for the WG to hear a detailed presentation on the pharmacopeia approach. Additionally the workshop included a presentation by the chair of the EAWG on coulometry analysis related to purity assessment. Liaising across the CCQM WGs in this field will be an ongoing priority.

A number of OAWG members attended the Protein and Peptide Therapeutics and Diagnostics (PPTD): Research and Quality Assurance International Workshop held in conjunction with the October 2018 OAWG meeting hosted by NIM. This was an excellent opportunity to interact with the clinical community and there was a strong focus on metrology aspects throughout the event, including a meeting between BIPM, IFCC and representative metrology institutes. There has been ongoing interaction with the IFCC community continuing on from this and leading to the IFCC-BIPM MOU signing in September 2020.

### 3.3. PROMOTING GLOBAL COMPARABILITY

For the period 2017-2020 the OAWG coordinated the Track A key comparisons as per its 10-year plan in Table A1. The WG has an ongoing programme coordinated by the BIPM to underpin the recognition of NMI/DI services in the highly important area of pure organic calibrators and calibration solutions. The WG runs a parallel suite of comparisons for matrix materials. The areas for these key comparisons were aligned with the priority areas flagged by the OAWG members for this period, i.e. clinical, food safety and food labelling.

**Table A1. Core Key Comparisons (Track A) carried out by OAWG in 2017-2020 period.** The area of the OAWG competency space is indicated followed by the specific model system selected to represent this in blue.

Year	Core Key Comparisons (Track A) Pure Materials and Calibration Solutions	Core Key Comparisons (Track A) Matrix Materials
2017	<b>CCQM-K78.a: Multi-component aqueous solution</b> [Aqueous Calibration; Mass > mg/kg; P] Amino acids ((L)-Phenylalanine, (L)-Leucine, (I)-Isoleucine, (L)- Proline)) in aqueous solution	<b>CCQM-K141: Polar analyte in high protein food</b> [Food: Mixed; Mass > mg/kg; P] Enrofloxacin and sulfadiazine in beef muscle
2018	<b>CCQM-K148.a: Non-polar pure organic</b> [Purity; MW 100-500; NP] Bisphenol A	<b>CCQM-K146: Non-polar analyte in high fat food</b> [Food: High fat; Mass > mg/kg; NP] Benzo[a]pyrene in olive oil
2019		<b>CCQM-K159: Biomarkers in clinical matrix</b> [Clinical: Serum; Mass > µg/kg & > mg/kg; P/NP] Amino acids (DL-Leucine and DL-Phenylalanine) in plasma

2020		<b>CCQM-K168: Analyte in high carbohydrate food</b> [Food: Carbohydrate; Mass > µg/kg & > mg/kg; NP]  <a href="#">Trans-zearalenone in maize</a>
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The Core Key Comparisons (Track A) for pure materials and calibration solutions that will be coordinated by the BIPM aim to cover the core competencies required for the provision of pure organic and organic solution calibrators. These are a rolling suite of KCs that form part of the BIPM work programme.

*CCQM-K78.a (BIPM)*. The CCQM-K78.a model system selected was amino acids in aqueous solution. Participants were required to assign the mass fractions, expressed in µg/g, of phenylalanine (Phe), leucine (Leu), isoleucine (Ile) and proline (Pro) present in solution in 0.01 N hydrochloric acid. The content and analytical challenges of the selected analytes are representative of those for typical calibration solutions for polar organic analytes in aqueous solution. A satisfactory level of agreement of the results was obtained between participants and with the gravimetric values for amino acid content. In the cases where the agreement was not satisfactory, the participants were able to identify a technical cause for the inconsistency. The comparison demonstrated the trueness and precision of double IDMS-based methods as a primary measurement procedure for the quantification of polar analytes in aqueous solution when an isotopically labelled version of the analyte is available as the internal standard. It also demonstrated that amino acid quantification using pre- or post-column derivatization with UV or FLD detection can provide results with comparable levels of performance. In this case, where the purity of the primary calibrators had been assigned with a relative standard uncertainty below 0.2%, results consistent with the KCRV within a relative expanded uncertainty in the range 1% - 2% could be realized and levels of 2%-4% were routinely achieved.

*CCQM-K148.a (BIPM)*. This was the first in the new K148 series covering the three areas of the organic purity measurement space. The ability to perform suitable purity assessment on the materials that an NMI either makes available to external users as pure substance reference materials or that are used by an NMI as their primary reference material for the assignment of the property values either of solution or matrix reference materials or for their reference measurement services is a core technical competency for the provision of measurement results in organic analysis traceable to the SI. The model system selected for this comparison was pure Bisphenol A. Seventeen NMIs participated in the comparison. The final report for this comparison is currently being completed.

Four Core Key Comparisons (Track A) for Matrix Materials were coordinated in this period.

*CCQM-K141 (NRC Canada)*. The measurands chosen as the model system were enrofloxacin and sulfadiazine in bovine tissue, two commonly used veterinary antibiotics. The bovine muscle tissue study material was derived from a single live animal that was administered with chemical based pharmaceutical agents prior to processing. Therefore, the study material was naturally incurred, providing a true test of extraction procedures relative to more commonly encountered spiked materials. Thirteen NMIs/DIs participated and the level of agreement was reasonable given the measurands and matrix were new for most laboratories. The KCRV values and their uncertainties at the 95% confidence level of  $57.81 \pm 2.57$  µg/kg for enrofloxacin and  $2285 \pm 68$  µg/kg for sulfadiazine were calculated using the DSL means. The comparison highlighted the complex challenges in extraction of these analytes effectively, in ensuring stability of solutions of analytes of this nature and in the equilibration of isotopically labelled internal standards for these types of analytes. The results for this comparison have been published.

*CCQM-K146 (NIM, China)*. Benzo[a]pyrene (BaP) is one of the markers for the occurrence of PAHs in foods, for which maximum residue limits are enforced in many countries. Edible oil and fats are the main source of human PAH intake. BaP may form in edible oils by pyrolytic processes, such as incomplete combustion of organic substances. Worldwide regulatory limits of BaP in edible fats and oils are from 2.0 µg/kg to 10 µg/kg. Comparable and traceable measurement results for BaP in oil are important worldwide. Thus BaP

in olive oil was the model system selected to align within the OAWG strategy. 16 NMIs/DIs participated. Different methods such as liquid-liquid extraction, GPC and SPE were applied in the sample pre-treatment and HPLC-FLD, HPLC-MS/MS, and GC-MS or GC-MS/MS were applied for detection by the participants. The Hierarchical Bayes option was selected for the KCRV value, which was determined as 2.74  $\mu\text{g}/\text{kg}$  with a standard uncertainty of 0.03  $\mu\text{g}/\text{kg}$ . The ten institutes that were included in the calculation of the consensus KCRV all agreed within their standard uncertainties.

*CCQM-K159 (LGC, UK)*. Babies diagnosed with amino acid disorders require constant monitoring of amino acid levels, especially for disease states such as phenylketonuria. In addition, amino acid measurement may aid in the evaluation of several other disorders such as neurological and nutritional disorders. The measurands for this study were the free amino acids, DL-Leucine and DL-Phenylalanine which were within the mass fraction range 1-1000 mg/kg. The matrix was frozen pooled human plasma (lithium heparin) which had been screened, bottled into 1.2 mL aliquots in screw capped vials and stored at  $-80^{\circ}\text{C}$ . The measurement of these samples is still underway.

*CCQM-K168 (NIM, China)*. Zearalenone (ZEN) is a fungal mycotoxin produced by *Fusarium* spp. and present in several types of food, especially in maize and wheat. It is a non-steroid estrogenic compound which may cause changes in reproductive organs, fertility loss and several other toxic effects. Zearalenone analysis is a matter of health and food safety for many countries around the world. Worldwide regulatory limits of ZEN in maize and its products are from 20  $\mu\text{g}/\text{kg}$  to 350  $\mu\text{g}/\text{kg}$ . The measurand of this study is trans-zearalenone in maize powder. Maize is a high carbohydrate and low protein, low fat matrix that falls within Sector 5 of the AOAC International food triangle. Maize materials were screened from a local supermarket, pulverized, sieved and homogenized at room temperature. The indicative range for the mass fractions of the analyte was 10-500  $\mu\text{g}/\text{kg}$ . Aflatoxin B1, ochratoxin A, fumonisin B1, etc. were also detected in the material as potential interferences. The measurement of these samples is still underway.

One other Track A report was published in the KCDB during this period. This was the complementary comparison to CCQM-K78.a, underpinning non-polar organic calibration solutions.

*CCQM-K131 (NIST, US)*. Polycyclic aromatic hydrocarbons (PAHs) result from combustion sources and are ubiquitous in environmental samples. The PAH congeners, benz[*a*]anthracene (BaA), benzo[*a*]pyrene (BaP), and naphthalene (Nap) were selected as the target analytes for CCQM-K131 in an acetonitrile solution. These targets span the volatility range of PAHs found in environmental samples and include potentially problematic chromatographic separations. Nineteen NMIs/DIs participated in CCQM-K131. The consensus summary mass fractions for the three PAHs were in the mass fraction range of (5 to 25)  $\mu\text{g}/\text{g}$  with relative standard deviations of 2.5 to 3.5 %.

The OAWG aims to co-ordinate a maximum of one Track C specialized comparison per year to cover areas that may represent particularly complex analytical challenges which a subset of the OAWG are working to address and/or be of particular international importance. Three Track C comparisons were published during this period.

*CCQM-K132 (NIST, US)*. Vitamin D is a fat-soluble vitamin that occurs primarily in two forms, vitamin D<sub>2</sub> and vitamin D<sub>3</sub>. Vitamin D is metabolized in the body to produce several closely related, hydroxylated species (metabolites), with 25-hydroxyvitamin D<sub>3</sub> [25(OH)D<sub>3</sub>] and 25-hydroxyvitamin D<sub>2</sub> [25(OH)D<sub>2</sub>] as the most common metabolites measured in human serum. Mass fractions of total vitamin D in human serum, calculated as the sum of 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub>, are typically low, in the 16 ng/g to 30 ng/g range. There has been international concern over the comparability of vitamin D measurements clinically, it is challenging because of its low level and the number of structurally similar metabolites. The OAWG's previous clinical comparisons had all been aimed at higher mass fraction levels and thus a Track C comparison was required to demonstrate capabilities. Seven NMIs/DIs participated in CCQM-K132. Participants evaluated the mass fractions, expressed in ng/g, of 25(OH)D<sub>3</sub>, 25(OH)D<sub>2</sub>, and 3-*epi*-25(OH)D<sub>3</sub> in two human serum materials, Pool I and Pool II. Due to the known low levels of 3-*epi*-25(OH)D<sub>3</sub> in both materials and the very low level of 25(OH)D<sub>2</sub> in Serum Pool I, the study protocol stated that KCRVs would be assigned only to 25(OH)D<sub>3</sub> in both materials and 25(OH)D<sub>2</sub> in Serum Pool II. Results for 3-*epi*-25(OH)D<sub>3</sub>

were requested to evaluate the separation technologies employed; 3-*epi*-25(OH)D<sub>3</sub> needs to be chromatographically separated from 25(OH)D<sub>3</sub> for proper quantification of 25(OH)D<sub>3</sub>. All participants used isotope dilution liquid chromatography with tandem mass spectrometry detection (ID LC-MS/MS) for the measurement of the vitamin D metabolites. The results generally agreed very well.

*CCQM-K138 (UME, Turkey)*. Mycotoxins in food are a major international food safety issue, they also represent a specific technical challenge in that they are toxic at very lower levels. The analytes in CCQM-K138 were the aflatoxins AFB<sub>1</sub>, AFB<sub>2</sub>, AFG<sub>1</sub> and AFG<sub>2</sub> (and their total) in fig. Nine NMIs/DIs participated. The CCQM-K138 results ranged from 5.17 to 7.27 ng/g with an %RSD of 10.5 for AFB<sub>1</sub>, from 0.60 to 0.871 ng/g with an %RSD of 11.7 for AFB<sub>2</sub>, from 1.98 to 2.6 ng/g with an %RSD of 10.4 for AFG<sub>1</sub>, from 0.06 to 0.32 ng/g with an %RSD of 36 for AFG<sub>2</sub>, and from 8.29 to 10.31 ng/g with an %RSD of 7.7 for Total AFs. All participants based their analyses on liquid chromatography, seven utilizing LC-MS/MS with labelled internal standards and two utilizing HPLC-FLD. Linear Pool estimators were used to assign the KCRVs for AFB<sub>1</sub>, AFB<sub>2</sub>, AFG<sub>1</sub> and AFG<sub>2</sub> and total aflatoxins. The relatively large RSDs for these results highlight the challenges in the analysis of these analytes.

*CCQM-K154 (NIM, China)*. The CCQM-K154.a and subsequent CCQM-K154.a.1 comparisons were coordinated by the BIPM and NIM) China within the BIPM's Mycotoxin Metrology Capacity Building and Knowledge Transfer (MMCBKT) project as part of its "Metrology for Safe Food and Feed in Developing Economies" Capacity Building Programme. This KC examined the ability to gravimetrically-prepare solutions having an assigned mass fraction of specified organic analyte as a Track C, Model II key comparison. The specific model system was: gravimetric preparation and value assignment of *trans*-zearalenone (*trans*-ZEN) in acetonitrile (ACN). Eleven NMIs/DIs participated in the, CCQM-K154.a and the Subsequent Comparison CCQM-K154.a.1. Participants were requested to gravimetrically prepare calibration solutions and value assign the mass fractions, expressed in mg/kg. The solutions and their certified values were then provided to the BIPM. The KCRVs, calculated from values measured by the coordinating laboratory based on calibrations obtained from independent gravimetrically prepared calibrant solutions, agreed with participants reported values, within their stated uncertainties. *trans*-ZEN was selected to be representative of non-polar Fusarium mycotoxins. It was anticipated to provide a challenge representative for the gravimetric preparation and value assignment of calibration solutions in the mass fraction range of 10 mg/kg to 100 mg/kg of mycotoxins with broadly similar structural characteristics. Six participants of the MMBCKT programme were provided with a stock solution having a known *trans*-ZEN mass fraction and expanded uncertainty to use to gravimetrically prepare and value assign a calibration solution. Four NMIs/DIs also participated using their own calibration solutions. The relative expanded uncertainties  $U(w_{KCRV})$  ranged from 0.90 % to 4.54 %. Inspection of the degree of equivalence plots for the *trans*-ZEN mass fraction assignments in CCQM-K154.a indicated that there was an excellent agreement of results in general.

Two further Specialized Key Comparisons (Track C) are still underway with their reports in preparation.

*CCQM-K133 (NIM China and NMIJ Japan)*. Phthalate esters (phthalates, PAEs) are widely used as plasticizers to enhance the durability, flexibility, and workability of plastics, especially Polyvinyl Chloride (PVC). Due to the nature of the physical binding of PAEs to polymers, they can easily be released from various products. These compounds have become ubiquitous in water, sediment, as well as food products and are classified as endocrine-disrupting chemicals because of their potential effect on wild animals and human beings. Recently, many countries prohibit or restrict the use of phthalates in electrical and electronic products, toys and children articles. CCQM-K133 assessed competencies for the analysis of "Low-Polarity Analytes in Plastics: Phthalate esters in Polyvinyl Chloride (PVC)" as this class of competencies was not covered under our Track A system. Nine NMIs/DIs participated and were requested to evaluate the mass fractions, expressed in mg/kg, of BBP in a low concentration PVC sample, and DBP, BBP and DEHP in a high concentration PVC sample, termed LCPVC and HCPVC. The consensus summary mass fractions for the four measurands are in the range of (95 to 905) mg/kg with relative standard deviation of 4 to 8 %.

*CCQM-K156 (UME Turkey)*. Perfluorinated alkyl substances (PFAS) such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been used in numerous industrial applications and products. However, because of their high stability, and resistance to biodegradation, atmospheric photooxidation, direct photolysis and hydrolysis, they have persistence in the environment. The PFAS/PFOS family of chemicals are a major environmental concern and are also technically challenging to measure, hence their selection for a Track C comparison. The measurands to be determined were the mass fraction of the linear forms for perfluoro-n-octanoic acid (L-PFOA) as acidic form and linear perfluoro-1-octane sulfonate (L-PFOS) as anion form in ground water. The indicative values were between mass concentration of 0.5 ng/kg and 10 ng/kg.

The OAWG also coordinated two Model 2 Comparisons examining the comparability of available and common CRMs/PT materials across the NMIs/DIs. These aim to cover key measurement areas where there are a number of materials available for the same (or very similar) measurand.

*CCQM-K142 (HSA, Singapore and NIST, US)*. This Model 2 comparison covered “Comparison of CRMs and Value-Assigned Quality Controls: Urea and Uric Acid in Human Serum or Plasma” and was the third Model 2 Key Comparison coordinated by the OAWG. CRMs certified for urea and/or uric acid content in human serum or plasma were compared using measurements made on these materials under repeatability conditions. Four NMIs/DIs submitted 10 CRMs certified for urea; five NMIs/DIs submitted 12 CRMs certified for uric acid. These materials represent most of the higher-order reference materials available then for these clinically important measurands. Uncertainty-weighted generalized distance regression was used to establish the Key Comparison Reference Function (KCRF) relating the CRM certified values to the repeatability measurements. The urea results for all 10 CRMs were considered to be equivalent at the 95 % level of confidence and were used to define the KCRF for urea. The uric acid result for one of the 12 CRMs was found to be non-equivalent: the submitting NMI re-evaluated the result and withdrew the material from use in defining the KCRF for uric acid. The remaining 11 CRMs were used to define the KCRF for uric acid. Monte Carlo methods were used to estimate 95 % level-of-confidence coverage intervals for the relative degrees of equivalence of materials,  $%d \pm U_{95} (%d)$ , and of the participating NMIs/DIs,  $%D \pm U_{95} (%D)$ . For the urea materials, the  $%D \pm U_{95} (%D)$  intervals were within (-3 to 5) % of the consensus results. For the uric acid materials from four of the five NMIs/DIs, the  $%D \pm U_{95} (%D)$  intervals were within (-4 to 5) % of the consensus results. These results demonstrated that with the exception of one material, the participating institutions could value-assign CRMs for urea and/or uric acid in human serum and plasma.

*CCQM-K147 (NIST, US and CENAM, Mexico)*. This Model 2 Comparison evaluated the value-assigned CRMs for niacin or niacinamide (vitamin B3) in milk powder and infant formula matrices. The materials were measured under repeatability conditions. Five NMIs/DIs submitted seven CRMs certified for niacinamide and two CRMs certified for niacin. Generalized Gauss Markov Regression (GGMR) and Bayesian methods were used to establish the Key Comparison Reference Function (KCRF) relating the CRM certified values to the repeatability measurements. The niacinamide and niacin results for all nine CRMs were deemed equivalent at the 95 % level of confidence and were used to define the KCRF for vitamin B3 (as niacinamide). Monte Carlo methods and Bayesian methods were used to estimate 95 % level-of-confidence coverage intervals for the relative degrees of equivalence of materials,  $%d \pm U_{95} (%d)$ , and of the participating NMIs/DIs,  $%D \pm U_{95} (%D)$ . The Bayesian method estimates were selected as the final DoE values. For the niacinamide and niacin materials, all of the  $%D \pm U_{95} (%D)$  intervals, were within (-10 to 10) % of the consensus results and all of these are statistically equivalent. These results demonstrate that the participating institutions can value-assign CRMs for niacinamide and/or niacin in milk powder and infant formula matrices.

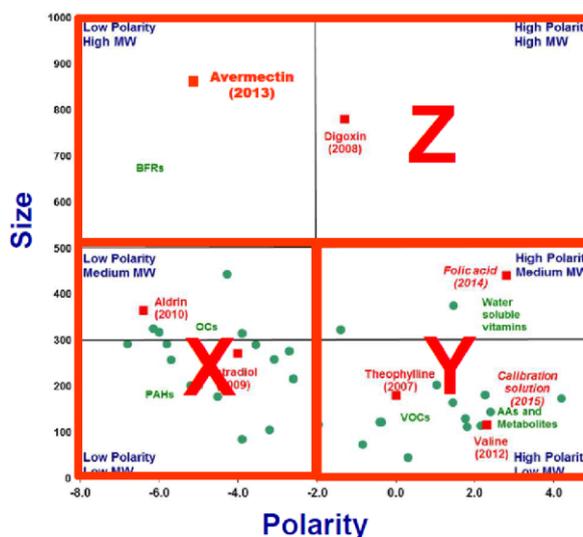
### **The OAWG Core competency approach**

During the 2017 to 2020 period the OAWG has been utilizing the core competency approach it outlined in its previous strategic plan. This is summarized below and was utilized in the selection of all of our Track A key comparisons:

The high-purity organics measurement space is defined as X (low polarity, small size), Y (high polarity, small size) and Z (all polarities, large size) as a “3-sector” organic purity model (Figure A1) which maps the organic purity space up to MW 1000:

- i. X : MW < 500,  $pK_{ow} < -2$
- ii. Y : MW < 500,  $pK_{ow} > -2$
- iii. Z : MW > 500

**Figure A1** Revised BIPM Model for future OAWG purity comparisons



The model for calibration solutions and matrix comparisons assumes that within a given matrix class the mass fraction of the analyte is the primary factor for the competency required to address measurement challenges specific to that matrix type, with the polarity of the analyte a secondary competency. The approach divides the matrices into four classes: 1) calibration solutions and low interference liquid matrices (organic, aqueous, water/beverages), 2) Clinical materials (serum, other), 3) Food (AOAC Food Triangle fat/protein/carbohydrate composition) and 4) Abiotic (soil, sediment, particulate and plastics). The proposed four matrix classes, which are further divided in eleven sub-classes, define a range of organic matrix material types sufficient to support current and emerging CMC claims.

These categories can then be used to define a set of comparisons. The classes reflect in particular the range of technical challenges involved in the value assignment of organic analyte mass fraction in food matrices. Four sub categories are identified to cover the range of necessary competencies. The focus on this area is justified by the high priority given by NMIs to the demonstration of competency and equivalence for the assessment of levels of contaminants and nutrients in a range of foodstuffs and primary produce.

Sitting under each of these four categories of matrices, the main measurement challenge was deemed to be mass fraction of analyte and thus this model considers four main ranges.

This can be defined as analyte Mass fraction ( $w$ ) into four sectors:

- 1) < 1  $\mu\text{g}/\text{kg}$ ;
- 2) between 1  $\mu\text{g}/\text{kg}$  and 1  $\text{mg}/\text{kg}$ ;
- 3) between 1  $\text{mg}/\text{kg}$  and 1  $\text{g}/\text{kg}$ ; and
- 4) between 1  $\text{g}/\text{kg}$  and 1  $\text{kg}/\text{kg}$

The previous OAWG model looked at polarity as a key parameter determining the measurement challenge, however this was felt to be of lower importance and thus is defined in this model as a secondary measurement challenge for analyte polarity in two main sectors:

- 1) polar (P) ( $pK_{ow} > -2$ )
- 2) non-polar (NP) ( $pK_{ow} < -2$ )

In practice not all mass fraction ranges are relevant for the different matrix classes, and the analytes of interest for a particular matrix are often limited to one polarity category (e.g., non-polar analytes in abiotic or high fat food matrices, polar analytes in aqueous calibration solutions). This reduces the effective number of comparisons needed to cover the competencies for the delivery of existing and anticipated CMC claims to the end of the next planning period to about twenty.

### **OAWG Broad Scope CMC Development**

The WG has developed a set of specific guidelines for broad scope CMCs that outlines the approaches taken with respect to the expected evidence for submission of claims and the expectations related to ongoing maintenance of such CMCs.

The OAWG approach assumes that broad scope CMC claims will normally fall into one of the following three classifications:

**Classification 1.** Homologues with identical functional groups and common classes with well-defined range of structural variation (in the same matrix type, if applicable). An example of a functional grouping is “Mass fractions of steroid hormones and a molar mass range of 100 - 500 g/mol at 10 - 500 ng/g levels in human serum” and of common class is “Polychlorinated biphenyls (PCBs) at mass fraction 100 µg/kg to 100 mg/kg in a soil matrix”.

**Classification 2.** Classes of analytes with greater structural diversity (In same matrix type if applicable). An example is “Mass fraction purity of low polarity pesticides ( $pK_{ow} < -2$ ) with a molar mass range 200 to 500 g/mol”.

**Classification 3.** Broad scope claim covering entire or major subset of the HFTLS statement

Examples are “Mass fraction purity of organic compounds of high polarity ( $pK_{ow} > -2$ ) with molar mass range 300 – 500 g/mol” for purity; “ Mass fraction of organic compounds of low polarity ( $pK_{ow} < -2$ ) with molecular mass of 100 – 500 g/mol at mass fraction from 100 µg/kg to 100 mg/kg in a multicomponent organic solution” for solutions and “High-polarity analytes ( $pK_{ow} > -2$ ) with the molecular mass range from 200 – 500 g/mol at mass fraction 20 – 5,000 µg/kg levels in a high fat, high protein matrix”.

The criteria of expected evidence for each of these three categories for organic pure materials, organic solutions and matrix materials are each clearly described in the guidance document. For example for matrix materials the Classification 1 broad scope CMC requirement is: “Successful participation in the most relevant OAWG Track A Model 1 key comparison with respect to the measurand plus 1 additional matrix comparison demonstrating uncertainty that supports the CMC claim to indicate repeat successful participation.” Whereas for a Classification 3 matrix material CMC the evidence is “Successful participation across at least 3 matrix comparisons” demonstrating uncertainties that support the CMC claim, one being an OAWG Track A Model 1 comparison related to the claim and the other two selected to be as closely related as possible to capabilities needed for the claim. “In the case of matrix materials the document also outlines the expectations with respect to capabilities to value assign the required calibration materials across the breadth of the broad CMC. These criteria will be taken into account in the OAWG planning of its next 10 years of key comparison to try and ensure that for priority areas for the WG that sufficient KC are planned to provide the required evidence. The document also covers expectations to demonstrate

ongoing competence and expected action if an institute performs poorly in a key comparison that forms part of the scope of any of their broad scope CMCs.

**The OAWG approach to broad scope CMCs is outlined in the two examples below:**

*NIST's Category 1 for Low Polarity Organic Compounds with MW <500 g/mol.* In CMC Cycle XX, NIST successfully submitted two broad CMCs for their Category 1 services on neat CRMs. The claims covered the entire HFTLS statements of Track A Model 1 key comparisons for high purity organic calibrators which rendered them "Classification 3" broad CMCs following the OAWG guidance document. The "low polarity" broad CMCs were based on performance (Degrees of Equivalence, DoEs) in CCQM-K55.a and CCQM-K55.b organic purity key comparisons, and further supported by successful participation in CCQM-K55.c and CCQM-K55.d covering "organic analysis space" outside of the CCQM-K55.a and CCQM-K55.b HFTLS statements. The range of claimed expanded uncertainties accounted for the uncertainties associated with the KCRV's for CCQM-K55.a and CCQM-K55.b. The claimed measurement techniques used were similarly employed with demonstrated success in the KCs. Further, comments were published in the KCDB to explain how traceability of the certified values is ensured in cases where the neat material is a salt. A listing of SRM numbers are also provided in the KCDB for ease of information to users of NIST's services. As NIST's specific Category 1 CMCs were voluntarily deleted in CMC Cycle XIX, there were none to be reviewed due to potential overlap.

*KRISS's Category 3 for Polybrominated Diphenyl Ethers (PBDEs,  $pK_{ow} < -2$  and MW <500).* In CMC Cycle XXI, KRISS successfully submitted nine broad CMCs for their category 3 services on organic solutions. Each claim covered specific classes of compounds without great structural diversity, further limited by defined polarity and molecular weight ranges, rendering them "Classification 1" broad CMCs. In the case of PBDEs in organic solutions, the broad CMC was adequately supported by KRISS's successful participation in CCQM-K131, a Track A Model 1 KC, and additional comparisons related to non-polar organic contaminants in solution and matrix samples (where the level of uncertainties are comparable to solutions), exceeding the minimum number of evidence required for a "Classification 1" broad CMC. The claimed mass fraction ranges, measurement uncertainties and measurement techniques used were covered by the HFTLS statements, accounted for the deviations from the KCRVs and were similarly applied in the KCs. KRISS also provided evidence from purity key comparisons (CCQM-K55 series) for their demonstrated capability to assign purity for the range of analytes within the broad matrix CMC. As KRISS's specific Category 3 CMCs were voluntarily deleted in CMC Cycle XXI, there was none to be reviewed due to potential overlapping.

**Interaction with RMO Activities**

OAWG members have had input into regional strategic planning via RMO activities such as the APMP focus groups. Similarly members have been heavily involved in key regional metrology programmes, such as relevant EMPIR projects. In some cases these have underpinned OAWG comparisons such as the PFOS/PFOA in groundwater key comparison. NMISA has been a driver of programmes within AFRIMETS, many of which are relevant to the OAWG with respect to food safety. NIM have co-ordinated two Track A OAWG comparisons and have aligned these with parallel programmes within APMP in order to gain maximum value.

## CASE STUDIES

### Case Study I: Primary Methods and Standards for Organic Measurements: qNMR<sub>IS</sub> and Related Techniques

Quantitative Nuclear Magnetic Resonance Spectroscopy utilizing internal standards based on <sup>1</sup>H nuclei (<sup>1</sup>H-qNMR<sub>IS</sub>) is considered a direct comparison method. The principle of qNMR is based on signal areas proportional to the molar amount of resonant nuclei of the analyte and standard. The qNMR primary method has become widely utilized for a considerable number of NMI/DIs in the OAWG (and PAWG) for SI-traceable chemical purity determination of pure organic, primary standards that are used in delivering organic-based measurement services. These primary standards play a critical role in directly promoting accuracy and worldwide comparability of measurement results produced by the chemical measurement community, supporting the soundness of clinical diagnostics, food safety and labeling, forensic investigation, drug development, biomedical research, and chemical manufacturing.

A major challenge for qNMR is to mitigate biases associated with unresolved impurity peaks that may result in overestimated mass fraction determinations when an analyte peak is not perfectly resolved. For larger molecules this becomes increasingly problematic as the spectrum generally becomes more complex. For analytes such as peptides or proteins, qNMR has a significant risk of purity determination error, because the impurities have similar amino acid residues as the major component, thus the impurity peaks are prone to overlap with the peaks of the major component. In this case, a peptide impurity corrected qNMR (PICqNMR) approach in which peptide impurities are subtracted from the total peptide content have been demonstrated recently. Other advanced qNMR approaches are being developed within select NMIs to improve the ability to effectively isolate the peaks to be used for quantitation of a measured substance from impurity peaks.

These advanced approaches can be considered as two distinct competences: 1) the combination of qNMR with liquid chromatographic separation, which includes direct hyphenation of HPLC to the qNMR method, an internal standard recovery correction approach for the HPLC-qNMR method, and an at-line approach that first purifies and collects the analyte via HPLC, followed by separate qNMR and HPLC analysis, and 2) quantification using multidimensional NMR techniques, such as quantitative heteronuclear single quantum correlation (qHSQC), ultrafast 2D-qNMR and quantitative diffusion ordered spectroscopy (qDOSY) applications. These are summarized in the Table below. Such approaches are intended to extend the application of qNMR to the molecular weight range (up to ≈ 6000 g/mol) of NMR-amenable analytes and potentially remove potential systematic errors through interference of overlapping peaks. This will ultimately improve the trueness of the qNMR method, thus expanding its application as both a metrological primary method and as a routine analysis method.

To further underpin the confidence in <sup>1</sup>H-qNMR<sub>IS</sub> as a reliable primary method for the OAWG, NMIJ coordinated two pilot studies for data acquisition and process in qNMR method (CCQM-P150 and CCQM-P150.b) in 2014 and 2017, respectively. Results of the pilot studies indicated that: (i) after data re-processing, the reported values were distributed within a small range (most of them within 0.5%) and (ii) between the participants, the difference of the estimated uncertainty components, such as variations in measurement and weighing were very large. The qNMR pilot studies and associated workshops on this technique have improved qNMR applications within NMIs and improved the understanding of typical best practice approaches to uncertainty estimation.

The CCQM-K55 series of Track A key comparisons and parallel CCQM-P117 pilot studies undertaken by the NMI/DIs in the OAWG have also examined qNMR. The methods used in CCQM-K55.d/P117.d (Folic acid) included 11 participants using only mass balance, 5 institutes utilizing both mass balance and qNMR approaches and 2 institutes using exclusively qNMR. The 4 pilot laboratories all used qNMR. The most recent pure substance Track A key comparison, CCQM-K148.a Purity of bisphenol A, has indicated the evolution of qNMR as a more routine primary method for NMIs/DIs, in that 9 institutes utilized both mass balance and qNMR for reporting results, with only 5 institutes using mass balance as the sole method.

In addition to Track A pure substance key comparisons and the CCQM-P150 pilot studies, several institutes have developed primary standards for use in  $^1\text{H}$ -qNMR<sub>IS</sub> measurements. The evaluation of seven internal standard reference materials (SRMs) to act as a 'universal' SI-traceable calibrator suite for organic compound purity determination by NMR spectroscopy was carried out by BIPM with other NMIs. In this programme, the goal was to develop an optimal parameter set for higher order  $^1\text{H}$ -qNMR measurements producing a relative standard uncertainty in the assigned value at the level of 0.1%. The parameters include relaxation delay, pulse offset, signal/noise, baseline and integration range, pulse width, spectral window, filter mode, acquisition time, window function.<sup>17</sup> Optimized conditions for acquiring qNMR spectra were developed and published, as well as the results of an extensive series of studies validating the use of the SRM suite to assign mass fraction values in four representative solvents ( $\text{D}_2\text{O}$ ,  $\text{DMSO-d}_6$ ,  $\text{CD}_3\text{OD}$  and  $\text{CDCl}_3$ ). Proper use and application of these SRMs results in standard uncertainties in the assigned values of the analyte of interest of the order of 1 mg/g in optimal cases.

An ultrapure and extensively characterized PS1 Benzoic Acid Primary Standard for qNMR was developed by NIST and serves as a definitive, primary reference (calibrant) that links the qNMR spectroscopy technique to SI units. As qNMR itself is a favorable method for accurate, direct characterization of chemical reference materials, PS1 is a standard for developing other traceable standards and is intended to establish traceability for the measurement of thousands of organic chemical species. Confidence in this link to the SI was established through (i) unambiguous identification of chemical structure; (ii) determinations of isotopic composition and molecular weight; (iii) evaluation of the respective molecular amount by multiple primary measurement procedures, including qNMR and coulometry; and (iv) rigorous evaluation of measurement uncertainty using state-of-the-art statistical methods and measurement models.<sup>18</sup> Similarly, NMIJ has developed a CRM 4601-a 3,5-Bis(trifluoromethyl)benzoic acid (3,5-BTFMBA) as a primary CRM for use in  $^1\text{H}$  and  $^{19}\text{F}$  qNMR also based on qNMR and coulometry. These types of internal standards certified with low uncertainties are highly valuable for the qNMR community.

Technique Class	Method	Advantages	Other Considerations
Hyphenated qNMR with chromatography	HPLC-qNMR with two-signal suppression	Suitable for compounds that can be completely resolved by HPLC	Suppression distortion needs to be decreased
	ISRC-HPLC-qNMR	Suitable for compounds that can be partially or completely resolved by HPLC	Good resolution and sensitivity in chromatography
Chromatography-assisted qNMR	HPLC-qNMR-HPLC method	Suitable for compounds that can be chromatographically purified	Good stabilization technique (if the purified sample is unstable).
	Extended Internal standard method (EIC)	Suitable for all compounds that can be completely resolved by HPLC, and the pure substances of structural related impurities are available.	Good resolution and sensitivity in chromatography; good identification technique for all structural related impurities.
	PICqNMR (peptide impurity corrected qNMR)	Suitable for compounds where structural-related impurities were identified and determined	Good identification technique for all structural related impurities
Multidimensional NMR	qHSQC	Suitable for compounds with isolated signals	Analyte specific bias to be determined
	UF (ultrafast) 2D	Suitable for separable components (i.e. metabolomic profiles)	Repeatability and recovery to be improved. Analyte specific bias to be determined
	qDOSY	Suitable for components with different diffusion characteristics (e.g., molecular size, shape)	Repeatability and recovery to be improved. Analyte specific bias to be determined

<sup>17</sup> Steven Westwood et al., *Metrologia* 56 (2019) 064001

<sup>18</sup> Nelson et al., *Anal. Chem.* 2018, 90, 17, 10510–10517, 2018

## Case Study II: PFAS – A Persistent Global Environmental Issue

Perfluorinated alkyl substances (PFAS) such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) have been used in numerous industrial applications and products, such as Aqueous Film-Forming Foams (AFFFs) for firefighting applications. Recent EU directives<sup>19</sup> for the ban of PFOA-containing AFFFs have been declared, however, there are countless areas where AFFFs have been routinely used and that remain contaminated (e.g. fire training sites, airports, military installations). As these compounds are relatively water soluble and effectively non-degradable, they readily migrate to surface and ground waters and are not effectively removed during conventional drinking water treatment, and thus present a significant public health risk.

The EU has proposed PFOA, its salts and PFOA-related substances that can be degraded to PFOA under environmental conditions, be included in the Annex A to the Stockholm Convention on Persistent Organic Pollutants (Council decision (EU) 2015/633).<sup>20,21</sup> As PFOS and PFOA in drinking water and food are the main human exposure pathways, the European Food Safety Authority (EFSA) established tolerable daily intakes (TDI) of 150 ng/kg body weight/day for PFOS and 1500 ng/kg body weight/day for PFOA.<sup>22</sup> Similarly, Food Standards Australia New Zealand (FSANZ) has established TDI of 20 ng/kg body weight/day for PFOS and 160 ng/kg body weight/day for PFOA.<sup>23</sup> Because of their adverse effects, a proposal for a Directive of the European Parliament and of the Council on the quality of water intended for human consumption has recast the EU Drinking Water Directive with a limit for sum of PFAS of 0.1 µg/L.<sup>24</sup> In Europe the current annual average environmental quality standard (AA-EQS) of PFOS concentration in inland and other surface waters is 0.65 ng/L and 0.13 ng/L, respectively. The maximum annual concentration EQS (MAC-EQS) is 36 µg/L in inland surface water and 7.2 µg/L in other surface waters.

A significant challenge exists to develop efficient, selective and accurate analytical methods for the differing PFAS compounds, including the range of isomers that exist. An international ILS<sup>25</sup> for PFASs in water and fish samples revealed that RSD values were 16%-69% and 22%-47% using mass-labelled internal standards. Results were strongly matrix dependent and varied significantly for the different PFAS compounds. Additionally, the ubiquitous nature of PFAS compounds in the environment, and in laboratory reagents, consumables, and the components within instruments necessitates extreme analytical controls to minimize background and contamination for reliable trace PFASs analysis. Furthermore, the ready adsorption of PFAS to sample handling devices and storage containers requires the design of single-use sample units to ensure that all mass is transferred prior to analytical processing and measurement.

In response to the growing need to establish comparability of PFAS measurements, in 2017 the CCQM approved the Track C key comparison CCQM-K156/P198 L-PFOA and L-PFOS in Ground Water. The CCQM-K156 key comparison and parallel pilot study was coordinated by UME and determined the mass fraction of linear perfluoro-n-octanoic acid (L-PFOA) in its acidic form and linear perfluoro-1-octane sulfonate (L-PFOS) in its anion form in ground water. There were seven participants. As limited calibration CRMs were available (NMIJ; CRM 4056-a (PFOA), CRM 4220-a (PFOS in Methanol)), the procurement and purity assessment with appropriate metrological traceability of native calibrants was the responsibility of many

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<sup>19</sup> Commission Delegated Regulation (EU) 2020/784 of 8 April 2020 amending Annex I to Regulation (EU) 2019/1021 of the European Parliament and of the Council as regards the listing of perfluorooctanoic acid (PFOA), its salts and PFOA-related compounds

<sup>20</sup> Council Decision (EU) 2015/633 of 20 April 2015 on the submission, on behalf of the European Union, of a proposal for the listing of additional chemicals in Annex A to the Stockholm Convention on Persistent Organic Pollutants

<sup>21</sup> Council Decision (EU) 2015/633 of 20 April 2015 on the submission, on behalf of the European Union, of a proposal for the listing of additional chemicals in Annex A to the Stockholm Convention on Persistent Organic Pollutants

<sup>22</sup> Benford, D. et al., Opinion of the scientific panel on contaminants in the food chain on perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA) and their salts. EFSA Journal, 2008, 653, 1-131

<sup>23</sup> FSANZ, Food Standards Australia New Zealand's (FSANZ) report on perfluorinated chemicals in food. 2017

<sup>24</sup> [https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1583491875802&uri=CONSIL:ST\\_6060\\_2020\\_REV\\_1](https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1583491875802&uri=CONSIL:ST_6060_2020_REV_1)

<sup>25</sup> S.P.J. van Leeuwen, C.P. Swart, I. van der Veen, J. de Boer. Significant improvements in the analysis of perfluorinated compounds in water and fish: Results from an interlaboratory method evaluation study. Journal of Chromatography A, 1216 (2009) 401-409.

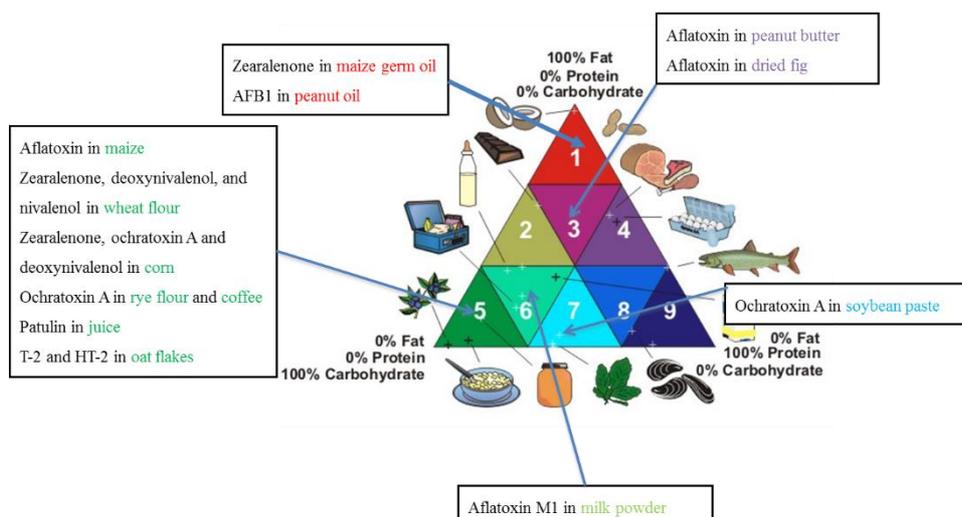
participants. The How Far the Light Shines Statement for the key comparison was formulated such that successful participation in CCQM-K156 demonstrates measurement capabilities in determining mass fraction of organic compounds, with molecular mass of 200 g/mol to 700 g/mol, having high polarity  $pK_{ow} > -2$  in mass fraction range from 0.5 ng/kg to 500 ng/kg in an aqueous media. These Track C comparisons that address trace level to ultra-trace level measurements of environmental pollutants of emerging concern are vital for NMI/DIs that need to demonstrate competency for their national environmental monitoring activities.

The demand is ever increasing for relevant matrix-based reference materials that are certified for contaminants of emerging concern, such as traditional and new persistent organic pollutants (e.g., PFAS), microplastics and plasticizers, and pharmaceuticals. The EMPIR project 14RPT03 “Matrix Reference Materials for Environmental Analysis” was coordinated by UME between 2015-2018 and was aimed at accelerating the development of Certified Reference Materials (CRMs) for environmental analysis, transferring knowledge between the NMI/DIs, and thus combining their skills and capabilities to advance environmental CRM production. Nine institutes participated in the project. One of the resultant CRMs of this project is UME EnvCRM 01 Organic pollutants (PFOS and PFOA) in Ground Water, which will provide laboratories with means to establish method QA/QC for PFAS in water measurements. Results were presented at the 14th International Symposium on Biological and Environmental Reference Materials at National Harbor, Maryland USA. A workshop “Matrix Reference Materials for Environmental Analysis” was also organized by TUBITAK UME on 10<sup>th</sup> of June 2015 under EMPIR 14RPT03 project. The JRC also has two matrix CRMs, IRMM-428 Water (PFASs) and IRMM-427 Pike-perch (PFASs in fish tissue) certified for various PFAS compounds.

### **Case Study III: Mycotoxins in Foodstuffs**

Mycotoxins are naturally occurring compounds produced by mold that grow on grains, feeds and cereal crops as well as nuts, fruits and coffee, often under warm and humid storage conditions. They are commonly present on such commodities; however, significant economic losses for food producers can ensue when mycotoxins are present at levels above maximum action levels and foodstuffs cannot be consumed and/or exported. A significant portion of OAWG activities are now focused on issues related to food security and food safety for the purposes of consumer protection and exports, as well as human and animal health protection. With mycotoxins being of significant global interest they have been the subject of several recent OAWG comparisons.

Accurate analytical measurement benchmarks for mycotoxins in various foodstuffs provide laboratory quality assurance and improved food quality control related testing against established maximum levels. This then strengthens the global food safety system. Comprehensive methods for mycotoxin analysis require sufficient sample extraction, carbohydrate and fat removal to minimize biases, and analytical detection specificity and selectivity, ideally utilizing IDMS methodology. Reliable matrix-based CRMs value assigned for mycotoxins are also a critical tool for accuracy control and to ensure analytical method validation. Currently available matrix CRMs for mycotoxins cover five sectors (1, 3, 5, 6, 7) of the AOAC food triangle, and include patulin in apple juice, ochratoxin A in rye flour, deoxynivalenol, ochratoxin A and zearalenone in corn, ochratoxin A in green and roasted coffee, aflatoxins (AFB1, AFB2, AFG1, AFG2, total aflatoxins) in both peanut slurry and maize, ZEN in maize (germ) oil and aflatoxin B1 in peanut oil. Typical high carbohydrate matrices account for 50% of the current matrix-based CRMs, as demonstrated in the Figure below.



Pure substance or solution-based certified reference materials utilized for calibration play a critical role in developing SI traceable measurement services. Because of the high toxicity of mycotoxins and difficulty to obtain, prepare and certify primary standards, only a small number of NMIs have developed relevant CRMs for calibration. Some mycotoxins are light and temperature sensitive, so strict transport and storage conditions are also needed. Pure substance CRMs of AFB1, ZEN, ZAN and T2 as characterized by mass balance and qNMR methods are available; pure deoxynivalenol is presently under development. The BIPM's Mycotoxin Metrology Capacity Building and Knowledge Transfer (MM CB&KT) project<sup>26</sup> aims to facilitate the capability of NMI/DIs to deliver national mycotoxin measurement services. Calibration solutions of five mycotoxins were prepared by gravimetry method and detected by HPLC-DAD.

The CCQM-K154 comparison series commenced in 2017 aimed to improve calibration solution preparation and value assignment of different types of mycotoxins. CCQM-K154.a "Zearalenone calibration solution" and CCQM-K154.b "Aflatoxin B1 calibration solution" are focused on the gravimetric preparation of solutions and analysis by UV spectrometry, HPLC-DAD and HPLC-MS/MS methods. Eleven NMIs/DIs participated in CCQM-K154.a comparison "Zearalenone calibration solution", and the degree of equivalence plots indicated there was an excellent agreement of results, with the exception of one NMI. This bias may have resulted from light-induced isomerization during the transportation timeframe.

A matrix-based Track C comparison CCQM-K138/P174 "Determination of Aflatoxins (AFB1, AFB2, AFG1, AFG2 and Total AFs) in Dried Fig" was coordinated by UME in 2015 and had nine NMI/DIs participants.<sup>27</sup> It was designed to allow the demonstration of capability for extraction, chromatographic separation, and quantification of low-mass fraction (< 0.1 ng/g) of multiple aflatoxins by HPLC-FLD or HPLC-MS/MS methods in dried food matrices. During sample preparation, immuno-affinity clean-up was largely employed, with analytical detection using either fluorescence detection or IDMS. Due to the CIPM MRA traceability requirements,<sup>28</sup> the results of four NMIs were excluded from KCRV determination, this highlighted the challenges in obtaining appropriate traceable calibrants for these analytes. Based on this Track C comparison, several NMIs submitted CMCs related to mycotoxins (aflatoxin B1, B2, G1, and total aflatoxins) in dried food, patulin in apple juice and ochratoxin A in coffee and wine.

The first Track A key comparison CCQM-K168 "Non-polar analytes in high carbohydrate food matrix: trans-Zearalenone in Maize Powder" was officially approved in 2020, and 13 institutes have signed up for the comparison. The comparison will demonstrate the capability in determining low-polarity analytes ( $pK_{ow} <$

<sup>26</sup> Guo, Z.; Li, X.; Li, H., Certified reference materials and metrological traceability assurance for mycotoxin analysis. Journal of AOAC International 2019, 102 (6), 1695-1707

<sup>27</sup> Bilsel, M.; Goren, A. C.; Gokcen, T.; Gunduz, S.; Koch, M.; Kakoulides, E.; Giannikopoulou, P.; Wai-tong, G. T.; Chan, A.; Kneeteman, E.; Mugenya, I.; Muriira, G.; Boonyakong, C.; Fernandes-Whaley, M.; Krylov, A.; Mikheeva, A., Report on key comparison CCQM-K138: determination of aflatoxins (AFB1, AFB2, AFG1, AFG2 and total AFs) in dried fig. Metrologia 2019, 56 (1A), 08008-08008.

<sup>28</sup> [https://www.bipm.org/cc/CIPM/Allowed/98/CIPM2009\\_24\\_TRAC\\_MRA\\_REV\\_13\\_OCT\\_2009.pdf](https://www.bipm.org/cc/CIPM/Allowed/98/CIPM2009_24_TRAC_MRA_REV_13_OCT_2009.pdf)

-2) with molecular mass range from 100 to 500 g/mol at mass fraction levels of 1 to 1000 µg/kg in a high carbohydrate food matrix. Additionally, an APMP pilot study and APMP-APAC-Joint PT will be conducted in parallel.

In 2015, NMISA launched The African Food and Feed Reference Material Program (AFFRMP) to specifically address analytical challenges testing laboratories face, through the provision of food and feed reference materials that are more accessible, affordable, and relevant to Africa. NMISA has also engaged with laboratories in the network to provide training on reference material production and methods of analysis for mycotoxins. PT schemes for mycotoxins in relevant matrices have been conducted within this network since 2018 (aflatoxins in peanut slurry), 2019 (aflatoxins in peanut butter, mycotoxins in maize) and in 2020 (aflatoxin M1 in milk). Within AFRIMETS, NMISA coordinated the NIM China APMP Zearalenone in maize proficiency test during 2019; participation of KEBS (Kenya) and ANM (Tunisia) in the PT is intended to prepare the NMI/DIs for successful participation in the CCQM-K168 trans-Zearalenone in Maize comparison in 2021.

Furthermore, NMISA has participated within the FAO-IAEA Africa Regional Food Safety Network (IAEA RAF5078 Phase II 2016-2019 and IAEA RAF5084 Phase III 2020-2023) to develop fit-for-purpose Africa-relevant training, reference materials and PT schemes enabling accurate food safety testing. This network comprises National Food Safety Monitoring laboratories representing 45 countries across the continent – who are the main stakeholders utilizing/benefiting from accurate methods of analysis, calibration CRMs, matrix CRMs and relevant PT schemes, to support critical food safety testing. The FAO-IAEA RAF 5084 project is aimed at achieving the UN Sustainable Development Goal 02 to end hunger, while achieving food security, improving nutrition, promoting sustainable agriculture, and enhancing food safety and consumer confidence through the supply of safe and competitive agricultural products.

The Food Safety Focus Group (FSFG) of APMP has collaborated with APEC in the capacity building in measurement and mutual recognition of mycotoxin in grain food. NIM has hosted two workshops in 2015 and 2017 with APEC to deliver the latest measurement methods for mycotoxins to improve the mycotoxins metrology capacity building and initiate APEC's long-term efforts to strengthen measurement and standards infrastructure in APEC region. Additionally, the international collaboration programme "Research and Application of Measurement Standard and Technical System in Agro-product Safety" was hosted by NIM to facilitate the cooperative development of both pure substance and matrix-based CRMs for food safety. NIM provided training opportunities to NMI/DIs and other science institutes for capacity building in CRM production. Participants from DSS (Thailand), HSA (Singapore), NIMSA (South Africa), VMI (Viet Nam), NPSL (Pakistan) STD-ITDI (Philippine), INMETRO (Brazil) and INTI (Argentina) have joined these long-term training activities. As a result, NIMSA and HSA have launched regional PTs for mycotoxins in grains and foodstuffs, in partnership with NIM. This project not only improved their capability in the production of CRMs but also promotes the establishment of mycotoxin metrological traceability systems in their economies.

#### **Case Study IV: Measurement Services Supported by OAWG Key Comparisons on Clinically Relevant Small Molecule Organic Biomarkers**

Over two decades, the OAWG has aimed to ensure the accuracy and comparability of global clinical measurements by conducting designated key comparisons of representative small molecule organic biomarkers that can cover a broad analytical space. The biomarkers were selected to have differing analytical challenges and mass fraction levels. This demonstration of NMI/DI competencies should lead on to distribution of effective services that will minimize the wastage of repeat testing and unnecessary therapy to create a sustainable healthcare industry. These key comparisons include the CCQM-K6 series for cholesterol in serum, CCQM-K11 series for glucose in serum, CCQM-K12 series for creatinine in serum, CCQM-K63 series for hormones in serum, CCQM-K132 for vitamin D in serum and CCQM-K109 for urea and uric acid in serum. In addition, the CCQM-K55 series of comparisons, which involve the purity

assignment of a range of organic compounds underpins the accuracy of the primary calibrators used for the measurement of these biomarkers.

Through participation in the key comparisons, NMI/DIs were able to realize metrological traceability and demonstrate the equivalence of their measurement capabilities. Many of the institutes are providers of certified reference materials that benefit the in-vitro diagnostic (IVD) industry, reference laboratories (e.g., calibration services) and the clinical chemistry and diagnostic testing laboratories. NMI/DIs are the largest contributors to CRMs listed on the JCTLM database. The reliability of their CRMs was also confirmed through two Model 2 CRM comparisons, CCQM-K80 creatinine in human serum and CCQM-K142 urea and uric acid in serum and plasma.

Additionally, the key comparisons organized under the auspice of the CCQM further qualified reference measurement procedures that exist in the JCTLM database. Examples include IDMS methods for the measurements of creatinine in serum by NIST, NIM and LGC; and glucose in serum by NIST and HSA. The commercial sector such as IVD manufacturers can then utilize the services of a reference measurement service provider listed in the database and be compliant with the EU, without having to invest in costly analytical instrumentations and manpower.

Besides CRMs, NMI/DIs are also providers of value-assignment services, for example, through provision of target values in accuracy-based External Quality Assessment Schemes (EQAS). Examples include Vitamin D External Quality Assessment Scheme (DEQAS) and the NIST/NIH Vitamin D Metabolites Quality Assurance Program (VitDQAP); these programmes have been deemed vital in advancing the quality of laboratory medicine and hence, patient care. Unlike programmes utilizing target values based on consensus, accuracy-based programmes base target values on higher-order methods (e.g., ID-LC-MS/MS) and thus are less biased by IVDs that may participate in the programme. Accuracy-based programmes also serve to reveal biases between method-specific consensus values associated from different analytical platforms and encourage manufacturers to improve their methods to a point where clinicians can confidently make use of results from any platform for accurate diagnosis, treatment or dosage adjustments.

#### **4. DOCUMENT REVISION SCHEDULE**

*OAWG Strategic Plan 2021-2030: V1, 20 December 2020*

## NON-CIPM ABBREVIATIONS

ACC	Africa Codex Committee
AACC	American Association for Clinical Chemistry
AfCFTA	Africa Continental Free Trade Area
AFG2	Aflatoxin G2
ANSES	French Agency for Food, Environmental and Occupational Health & Safety
APAC	Asia Pacific Accreditation Cooperation
APEC	Asia-Pacific Economic Cooperation
ARSO	African Organization for Standardization
AUC	African Union Commission
BTEX	Benzene, Toluene, Ethylbenzene, Xylene mixture
CIC	Compound independent calibration
CEN	European Committee for Standardization
DEA	Drug Enforcement Administration (US)
DSC	Differential scanning calorimetry
EBM	Effect-based monitoring
EDC	Endocrine disruptor compound
EMN	European Metrology Networks
EMPIR	European Metrology Programme for Innovation and Research
EMRP	European Metrology Research Programme
EPAs	Environmental Protection Agencies
EQAS	External Quality Assurance Services
FAO	Food and Agricultural Organizations of the United Nations
FDA	Food and Drug Administration (US)
GGMR	Generalized Gauss Markov Regression
GPC	Gel permeation chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
HPLC	High Performance Liquid Chromatography
HRMS	High resolution Mass Spectrometry
ICHCLR	International Consortium for Harmonization of Clinical Laboratory Results
ICP-MS	Inductively Coupled Plasma mass spectrometry
IDMS	Isotope Dilution Mass Spectrometry
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IHM	Inventory of Hazardous Materials
ILC/ILS	Interlaboratory comparison/Interlaboratory study
ISO	International Organization for Standardization
IUPAC	International Union of Pure and Applied Chemistry
IVD	In vitro diagnostics
IVDR	In vitro diagnostic regulation
JCTLM	Joint Committee for Traceability in Laboratory Medicine
JCR	Joint Research Centre – European Commission
LC-MS	Liquid Chromatography-Mass Spectrometry
LOD	Limit of detection
MP	Microplastics
MOAHs	Mineral oil aromatic hydrocarbons

MOSHs	Mineral oil saturated hydrocarbons
PAEs	Phthalate esters
PAHs	Polycyclic aromatic hydrocarbons
PCBs	Polychlorinated Biphenyls
PFAS	Per- and polyfluoroalkyl substances
PFOA	Perfluorooctanoic acid
PFOS	Perfluorooctanesulfonic acid
PNEC	Predicted no-effect concentration
POPs	Persistent Organic Pollutants
PT	Proficiency testing
PTM	Post-translational modifications
qNMR	Quantitative Nuclear Magnetic Resonance Spectroscopy
RASFF	Rapid Alert System for Food and Feed
RELA	External quality assessment scheme for Reference Laboratories
Rili-BÄK	Guideline of the German Medical Association of Quality Assurance in Medical Laboratory Examinations
SPE	Solid phase extraction
SVOC	Semivolatile organic compound
WADA	World Anti-Doping Agency
WHO	World Health Organization
WMO	World Meteorological Organization