Report from the CCQM Task Group on Method-defined measurands

approved final report
2019/04/24

1 Background

At the 23rd meeting of the CCQM the President established a Task Group to develop a position paper describing the criteria used to decide which method-defined measurands and measurement services were in the scope of activities covered by the CCQM. The position paper shall provide guidance to ensure consistency and coherence of approaches in the key comparison database (KCDB) and prevent pure testing capabilities creeping into the database. At its 24th meeting the CCQM plenary supported the developed preliminary criteria and the Task group agreed to deliver a final report for the April 19 meeting.

Members of the Task Group are Dr. H. Andres, Dr. R. J. C. Brown, Dr. S. Ellison, Dr. H. Emons, Dr. B. Güttler, Prof. H. Li, Dr. Z. Mester, and Dr. J. Morrow and Dr. R.I. Wielgosz.

2 Definition of Method-defined measurands

The standard ISO 17034: 2016 defines operationally defined measurand (or method-defined measurand) in clause 3.7 as follows: An ***operationally defined measurand is a measurand that is defined by reference to a documented and widely accepted measurement procedure to which only results obtained by the same procedure can be compared.*** In the note 1 to the clause, the examples of crude fibre in foods, impact toughness, enzyme activities and extractable lead in soils are mentioned.

3 Examples

There are numerous examples of method-defined measurands, some of which already appear in the KCDB. For example, hardness, a measurand studied in CCM comparisons, is regularly included. Examples relevant to chemical and biological measurement are given in Table 1:

Table 1: List of method-defined CCQM measurands with/without entries in the appendix B/C of the KCDB.

Method-defined measurand	**Appendix B KCDB**	**Appendix C KCDB**
BET (Brunauer–Emmett–Teller theory) specific surface area of a material	yes, e.g. CCQM K136	yes
pH	yes, e.g. CCQM K18	yes
particles number concentration in air	yes, e.g. CCQM K150	yes
catalytic activity of enzymes	yes, e.g. CCQM P137	no
Amount of (or mass fraction of) moisture in grain	no	no
Protein content in blood by ELISA	no	no
Amount of TOC (total organic carbon) in a material	no	no
Total protein content in a food/feed sample as measured by the Kjeldahl method	no	no

The first three example method-defined measurands have associated CMCs currently published in Appendix C of the KCDB:

- ***BET specific surface area of a material***:
  ISO 9277:2010 specifies the determination of the overall specific external and internal surface area of disperse (e.g. nano-powders) or porous solids by measuring the amount of physically adsorbed gas according to the Brunauer, Emmett and Teller (BET) method. It takes account of the International Union for Pure and Applied Chemistry (IUPAC) recommendations of 1984 and 1994. Clause 9 of the Standard refers to certified reference materials for the BET method provided by national metrology institutes and other organisations.
- ***pH***
  The pH is defined thermodynamically as the negative logarithm of the hydrogen activity $a(H^+)$. This single ion quantity is immeasurable by any thermodynamically valid method. The International Union for Pure and Applied Chemistry (IUPAC) thus recommended in 1984 and specified more precisely in 1994 for pH measurements in dilute aqueous solutions in the temperature range 5–50 °C the following convention: Primary realisation of pH involves the use of a cell without transference, known as the Harned cell. The value of $\gamma(Cl^-)$ in the extrapolated acidity function $a(H^+)\,\gamma(Cl^-)$ is calculated using the Bates–Guggenheim convention based on Debye–Hückel theory. This international agreement provides an operational definition of pH for the realisation of primary pH standards. In the 2002 IUPAC recommendation the possibility to achieve full SI traceability by adding an uncertainty for the Bates-Guggenheim convention is described.
- ***Particle number concentration in air***:
  ISO 27891:2015 describes methods to determine the detection efficiency of condensation particle counters (CPCs) at particle number concentrations ranging between 1 cm^{-3} and 10^5 cm^{-3}, together with the associated measurement uncertainty. The particle sizes covered by the methods described in this International Standard range from approximately 5 nm to 1000 nm. If a source of singly-charged particles is used, number concentration (in cm^{-3}) is directly proportional to charge concentration (e.g. in $fC \cdot cm^{-3}$). The Standard refers to the role of NMIs in providing certification for both reference aerosol electrometers and reference CPCs.

The next two examples have been the subject of CCQM or RMO led comparisons but currently do not have associated CMC entries:

- ***Catalytic activity of enzymes***:
  ISO 17511 describes calibration hierarchies with traceability to a primary reference measurement procedure that define the measurand. Seven such reference measurement methods for catalytic activity of enzymes (e.g. α-amylase) by kinematic spectrophotometry at 37 °C have been developed and internationally agreed by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). These have been reviewed and found compliant with ISO 15193 requirements for reference measurement procedures and are listed in the Joint Committee on Traceability in Laboratory Medicine (JCTLM) database. Up till now eleven reference measurement service providers (accredited calibration laboratories) (6 in China and 5 in Europe) are listed in the JCTLM database. No reference to the role of CIPM MRA signatories is given in the IFCC procedures, however five NMIs participated in the

CCQM-P137 comparison of α-amylase catalytic activity in serum organized in 2016 by NIM, China.

- ***Amount of moisture in grain***:
  The International Recommendation OIML R-59 : 2016 on Moisture meters for cereal grains and oilseeds states in Part 1 clause 4.3 that the national air oven methods to determine grain moisture content vary widely in procedures and results. Due to the lack of an agreed international standard responsible national bodies define legally the reference method. In the past CCQM already pointed out that a prerequisite for its involvement is an international agreement on the reference method. RMO comparisons were performed in COOMET, e.g. COOMET 436/RU/08 and COOMET 479/RU/09.

The remaining example are well known method defined measurands for which there are currently no CMCs and which have not been the focus of any CCQM or RMO comparisons so far.

- ***Protein content in blood by ELISA:***
  In an enzyme-linked immunosorbent assay (ELISA) proteins are quantified through a specific interaction with immobilized antibodies or antigens. Results differ among test kits and from those obtained by mass spectrometric approaches as the interaction is dependent on the antibodies/antigens and the conformational structure of the protein ("mobiloform"). No international agreed reference method for protein quantification is listed by the Joint Committee on Traceability in Laboratory Medicine (JCTLM).
- ***Amount of TOC in a material:***
  The ISO 8245:1999 defines total organic carbon (TOC) as the sum of organically bound carbon present in water, bonded to dissolved or suspended matter, including cyanate, elemental carbon and thiocyanate. The standard requires calibration of comparison with potassium hydrogen phtalate (KHP) standard solution. For certain high purity materials, the mass fraction of carbon of KHP equals the TOC content. In general, ubiquitous carbonaceous impurities add to the TOC content.
- ***Total protein content by Kjeldahl method:***
  This continues to be a topic of discussion at international level, e.g. at the recent Codex Committee for Nutrition and Foods for Special Dietary Use (CCNSFDU) the question about what the correct protein conversion factor for Kjeldahl has arisen. The method measures total (by method) nitrogen content, which is used as a surrogate for protein in food samples, by converting with an agreed conversion factor, which itself depends on the food type under analysis.

4 CCQM Terms of Reference

The CCQM is responsible for developing, improving and documenting the equivalence of national standards (certified reference materials and reference methods) for chemical and biological measurements. It strives to progress the state of the art of chemical and biological measurement science and to work with global stakeholders to promote and increase the impact of metrology in chemistry and biology. It advises the CIPM on matters related to chemical and biological measurements including advice on the BIPM scientific programme activities.

The objectives of the CCQM are:

a. to progress the state of the art of chemical and biological measurement science (including contributing to the establishment of a globally recognized system of national measurement standards, methods and facilities for chemical and biological measurements; and acting as a forum for the exchange of information about the research and measurement service delivery programmes and other technical activities of the CC members and observers, thereby creating new opportunities for collaboration)

b. to reach out to new and established stakeholders (facilitating dialogues between the NMIs and global stakeholders in order to define new possibilities for metrology in chemistry and biology to deliver impact)

c. ***to demonstrate the global comparability of chemical and biological measurements (through promoting traceability to the SI, and where traceability to the SI is not yet feasible, to other internationally agreed references***; contributing to the implementation and maintenance of the CIPM MRA with respect to chemical and biological measurements; reviewing and advising the CIPM on the uncertainties of the BIPM's calibration and measurement services as published on the BIPM website)

5 Decision Criteria

Considering the CCQM terms of reference it is proposed that all the following requirements shall be met as agreed by consensus of the CCQM for method-defined measurands and measurement services to be considered in the scope of activities covered by the CCQM, and eligible for CMC claims in the BIPM KCDB:

a. The method-defined measurand must be within the remit of CCQM
The remit of CCQM, as defined in its terms of reference.

b. The method-defined measurand must be internationally agreed and specifically defined in the field of application.
This demonstrates the global interest in the measurand and the need for international equivalence. Methods agreed only at a national or regional level are not acceptable.

c. The method-defined measurand must be a stable reference point in time.
References in the method shall be clearly defined and reproducible over time and not dependant on a specific (reference) material.

d. The method, as applied at the relevant NMI or DI, is considered as the highest metrological reference within a calibration hierarchy.
The NMI's or DI's measurement service shall disseminate metrological traceability. Routine test methods and data processing algorithms are out of scope.

If a method-defined measurand and measurement service fails to meet the criteria, a narrower definition of the measurand that would pass the criteria is recommended.

6 Implementation

The task group proposes to implement the decision criteria after formal approval by CCQM.

Annex 1: Review of examples against decision criteria

	Decision criteria/requirements for considering method-defined measurand within CCQM scope				
Method-defined measurand	Remit of CCQM?	Method internationally agreed?	Stable reference point in time?	Highest metrological reference within a calibration hierarchy?	**Can be included as a CMC in BIPM KCDB?**
pH	**YES**	**YES** *IUPAC 1994 recommendations*	**YES** *Measurement equation quantities SI traceable other than 1 conventionally defined parameter*	**YES** *Value assignment of primary buffers for value assignment of secondary and tertiary standards for calibration of glass electrodes*	**YES**
particles number concentration in air	**YES**	**YES** *ISO 27891:2015 describes methods*	**YES** *Measurement equation quantities SI traceable and multiple-charge correction defined*	**YES** *Role of NMIs as highest reference point in calibration clearly described in standard*	**YES**
catalytic activity of enzymes	**YES**	**YES** *For 7 IFCC reference methods (measurands)*	**YES** *Measurement equation quantities SI traceable with reaction conditions conventionally defined*	**YES** *Highest order reference in ISO 17511 compliant calibration hierarchy for enzyme catalytic activity*	**YES**
BET (Brunauer–Emmett–Teller theory) specific surface area of a material	**YES**	**YES** *ISO 9277:2010 describe method*	**YES** *Measurement equation quantities SI traceable expect BET-isotherm*	**?** *Certified reference material used for method validation*	**?**
Amount of (or mass fraction of) moisture in grain	**?**	**YES** *International Recommendation OIML R-59 : 2016*	**NO** *National air oven methods to determine grain moisture content vary widely in procedures and results*	**?** *reference for legal metrology applications*	**NO**
Protein content in blood by ELISA	**YES**	**NO** *No IFCC reference methods (measurands)*	**NO** *Test kits sensitive to different "mobiloforms", issues with property rights*	**NO** *No IFCC reference methods (measurands)*	**NO**
Amount of TOC (total organic carbon) in a material	**YES**	**YES** *ISO 8245:1999 describes method*	**NO** *material dependent parameter*	**NO** *Certified reference material used for method validation*	**NO**
Total protein content in a food/feed sample as measured by the Kjeldahl method		**YES** *Codex Alimentarius reference method*	**NO** *Dependent on protein correction factors*	**NO** *Certified reference materials used for method validation*	**NO**

Annex 2: Further examples against decision criteria

Method-defined measurand	**Decision criteria/requirements for considering method-defined measurand within CCQM scope**
Hardness	No, not in the remit of CCQM
Surface area by BET	No, not considered as highest metrological reference within a calibration hierarchy → define measurand as amount of nitrogen / argon adsorbed on a surface
Pore size by BET	No, not in the remit of CCQM
Amount of gold by fire assay	No, not considered as highest metrological reference within a calibration hierarchy
Soluble or leachable metals in particulates	No, method not internationally agreed and not stable in time
Film thickness	No, not in the remit of CCQM → define measurand as amount of element in matrix
Ethanol mass concentration in wet air by Dubowski	No, method not internationally agreed
Total sulphur / hydrocarbons in hydrogen	No, method not internationally agreed
Total protein content in a food/feed sample as measured by the Kjeldahl method	No, not a stable reference point in time and not considered as highest metrological reference within a calibration hierarchy → define measurand as amount of nitrogen in a food/feed sample