International comparisons on organic analysis. The main achievements and development perspectives

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Abstract: International comparisons in organic analysis (OA) are organized and coordinated by the Organic Analysis Working Group (OAWG) of the Consultative Committee for Amount of Substance (CCQM). OAWG also performs strategic planning and highlights the focus areas and challenges in OA. Realizing well that the amount of organic compounds and potential combinations of analyte-matrix is numerous, the OAWG has developed a systematic approach to the comparisons organizing. This approach allows to comprehensively describe the specifics of each comparison and appropriate features combination allows to cover all relevant aspects of OA. In terms of CMCs submission, recently the new concept has been created suggesting a broader view on the NMIs competence – it is the concept of "Broad Scope Claims" (BCs). BCs allow NMIs to submit CMCs for a wider range of analytes and matrices. In 2021 the OAWG has highlighted the priority areas for activities and promising methods and technologies for the OA for the period up to 2030. In international comparisons on OA Russia is represented by VNIIM. Since 1998 VNIIM has been taking part in more than 35 comparisons covering various aspects of OA. Each successful comparison is a real and documented confirmation of Russia competence in the relevant OA area. At the moment 89 CMCs are presented in the Database, including 25 BCs.

International comparisons in organic analysis (hereinafter - OA) are organized and coordinated by the Organic Analysis Working Group (OAWG) of the Consultative Committee for Amount of Substance (CCQM). The OAWG also performs strategic planning and highlights the focus areas and challenges in OA [1].

Historically, comparisons were organized to support specific types of metrological services and the link between comparisons and calibration and measurement capabilities (hereinafter - CMCs) was direct - "substance-to-substance-matrix-to-matrix" and the scope of claims of each comparison was clearly defined and narrow. Later it became obvious that such working design leads to increasing the number of comparisons (with the expansion of NMI metrological service) and reducing the number of participants due to high resource consumption. This situation demanded, firstly, a systemic approach to the planning of comparisons and, secondly, a complex solution regarding the scope claims of performed comparison.

The first task has been solved through systematization - all comparisons in the OA area were characterized using several key features. Thus, in addition to the division into parts A, C and D established in the CCQM, all key and pilot comparisons in organic analysis are systematized based on three basic characteristics: analyte type, matrix type, range (level) of analyte(s) content. This approach allows to comprehensively describe the specifics of each comparison and appropriate features combination allows to cover all relevant aspects of OA [2].
Analyte type.
The OAWG separated pure organic substances into groups according to their basic physicochemical properties and, thus, created a model of the organic analysis space. This model looks like a coordinate system, where the abscissa represents the logarithm of substance distribution coefficient in the water-octanol system, pKow (from minus 8.0 to 4.0), which directly characterizes the degree of hydrophobicity and/or hydrophilicity of an organic compound, and the ordinate is the molar mass of the compound (from the minimum to 1000).

Matrix type.
The basic classification of matrices is fixed in the categories established in CCQM, an extra classification within the framework of the OAWG involves the matrices division into four classes and eleven sub-classes, which are sufficient for a comprehensive description of the samples (see Table 1).

Range (level) of the component(s) content.
The OAWG considered it expedient to identify four quantitative ranges (see Table 2). The analyte content determines the analytical method choice, the sample preparation method and also directly affects the measurement uncertainty.

Table 1. Matrix classes, divided in eleven sub-classes

| Classes                                      | Sub-classes               |
|----------------------------------------------|---------------------------|
| 1. Calibration solutions and low interference liquid matrices | 1.1 organic solvent calibration solutions |
|                                              | 1.2 aqueous solvent calibration solutions |
|                                              | 1.3 waters, beverages etc |
| 2. Clinical materials                        | 2.1 serum/plasma          |
|                                              | 2.2 other (skin, hair, etc.) |
| 3. Food                                      | 3.1 > 60% fat* (Food Triangle Categories 1,3) |
|                                              | 3.2 > 60% protein* (Food Triangle Categories 8,9) |
|                                              | 3.3 > 60% carbohydrate* (Food Triangle Categories 5,6) |
|                                              | 3.4 mixed matrix (no component present > 60 % (Food Triangle Categories 2,4,7) |
| 4. Abiotic                                   | 4.1 soil, sediment and particulate |
|                                              | 4.2 other (plastics, etc.) |

Table 2 - Analyte Mass fraction (w)

| Level     | Mass fraction range            |
|-----------|--------------------------------|
| Very high | 1 g/kg < w < 1 kg/kg           |
| High      | 1 mg/kg < w < 1 g/kg           |
| Low       | 1 μg/kg < w < 1 mg/kg          |
| Very low  | w < 1 μg/kg                    |

To solve the second task a fundamentally new approach has been created suggesting a broader view on the NMIs competence. Instead of the previously rule "substance-to-substance-matrix-to-matrix" OAWG has introduced into practice the concept of "How Far the Light Shines" (hereinafter - HFTLS), which combines various options for the same type of measurements. Recently, next step has been made towards the optimization and efficiency - the concept of "Broad Scope Claims" (hereinafter - BCs) has been developed and implemented. BCs concept allows NMIs to submit CMCs for a wider range of analytes and matrices.

Of course, the convincing arguments and supporting evidences and positive history of participation in relevant comparisons and previously confirmed CMCs in similar categories are required for the BCs approval. The criteria for the BCs submission and approval in the field of OA are documented in OAWG
document - Criteria for broad scope claims with the Organic Analysis Working Group (OAWG), Version 2.2 [3].

The emergence of the BCs concept opens up the opportunity for NMIs to significantly expand the area of metrological service. At the same time, the absolute number of CMCs in the BIPM database will be reduced, which should ease the bureaucratic burden on CCQM and make the database more functional and convenient for consumers. This emerging trend reflects the current moment and the long term perspective.

When planning comparisons, the OAWG takes into account the relevance of research, existing metrological service, promising directions and technologies etc.

In 2021, the group developed a fundamental document, which highlighted the priority areas for the OAWG activities and identified promising methods and technologies for the development of metrology in the OA for the period up to 2030 - Consultative Committee for Amount of Substance – Metrology in Chemistry and Biology Working Group on Organic Analysis: Strategy 2021-2030 [4].

The OAWG has set the highest priority for the Food Sector category, since food safety and authenticity are directly related to the quality of people life in all countries.

The Clinical Sector has been and remains the long term area of emphasis for the OAWG due to medical decisions about the care of specific patients are made on clinical results. In addition, the general global trend for the development of digital medicine requires appropriate metrological service.

The Environment Sector was rated as a lower priority by the OAWG members, but niche areas were highlighted where there are serious problems with specific toxicants (e.g. persistent organic pollutants - POPs).

As new priorities, the OAWG has identified the measurement of pharmaceutical and narcotic substances in the interests of forensic medicine and anti-doping control - Forensic Chemistry and Anti-Doping, as well as work with Manufactured Materials and Industrial Products, including the study of microplastics.

Among the promising analytical methods, the absolute first place is occupied by quantitative Nuclear Magnetic Resonance (qNMR) for the purpose of organic compounds purity determining. It is a worthy alternative to the traditional mass balance approach. NMR spectroscopy has long been known as the leading method for the qualitative structural analysis of organic molecules, but for quantitative analysis, the NMR potential was recognized recently, and at the moment the possibilities of qNMR are being actively studied.

Other OAWG activities are related to high-resolution mass spectrometry (HRMS) and the development of metrological support for non-targeted analysis.

A specific important area of the OAWG activity is harmonization of NMI approaches to the uncertainty budget formation and calculation, including the contributions from hidden sources - dark uncertainty.

In international comparisons on OA Russia is represented by VNIIM. Since 1998 VNIIM has been taking part in more than 35 comparisons covering various aspects of OA. As an example, Table 3 shows a list of key comparisons over the past 5 years, which clearly demonstrates the variety of tasks in organic analysis.

| Primary calibration                                                                 | Accuracy control                                                                 |
|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| CCQM-K78.a: Mass Fraction of Amino Acids in acidic solution                        | CCQM-K141 Enrofloxacin and Sulfadiazine in Bovine Tissue                           |
| CCQM-K148.a: Characterization of Organic Substances for Chemical Purity: Bisphenol A | CCQM-K146 Benzo[a]pyrene in Olive Oil                                             |
| CCQM-K78.b Pesticides in organic solution                                          | CCQM-K133 Phthalate esters in Polyvinyl Chloride (PVC)                           |
Table 4 summarizes the CMCs of Russia on OA, including BCs. Each successful comparison and CMC into the Database of the International Bureau of Weights and Measures (Bureau International des Poids et Mesures - BIPM) is a real and documented confirmation of Russia competence in the relevant OA area and indicator of the Russian state primary standard GET 208 efficiency as well.

Table 4 – CMCs of Russia on Organic Analysis [5]

| CCQM category | Category name                              | CMCs (including BCs), 2021 |
|---------------|--------------------------------------------|----------------------------|
| 01            | High purity chemicals                      | 41 (2)                     |
| 03            | Organic solutions                          | 6 (3)                      |
| 13            | Sediments, soils, ores and particulates    | 17 (17)                    |
| 10            | Biological fluids and materials            | 9                          |
| 11            | Food                                       | 9 (3)                      |
| 09            | Advanced materials                         | 7                          |

Table 4 clearly shows that calibrators (pure organic substances and solutions of ones) make up more than half of the CMCs, which confirms their fundamental importance for the metrological traceability in organic analysis.

Thus, OA is a complex and special area of measurement, which requires suitable rules for international comparisons and CMCs. Thanks to the comparison systematization and concept of HFTLS and BC, the NMIs have got the opportunity to significantly expand the provided metrological service. In perspective, VNIIM plans to enlarge the CMCs by forming the BCs and to expand the metrological service in the area of pure substances and standard solutions by increasing the production of commercially available CRMs (Russian abbreviation - GSO or ГСО). Development and implementation of qNMR for direct measurement of the organic components purity - the next important item on the agenda.

References
[1] CCQM Strategy Document, Version 1.0 21.06.2021, Period covered: 2021-2030 (https://www.bipm.org/utils/en/pdf/CCQM-strategy-document.pdf)
[2] CCQM Organic Analysis Working Group Strategy Document, Date drafted: September 2017, Period covered: 2017-2026.
[3] Criteria for broad scope claims with the Organic Analysis Working Group (OAWG), Version 2.2, 2019-10-15
[4] Consultative Committee for Amount of Substance – Metrology in Chemistry and Biology Working Group on Organic Analysis: Strategy 2021-2030, 20 December 2020 (https://www.bipm.org/en/committees/cc/ccqm/wg/ccqm-oawg)
[5] KCDB BIPM https://www.bipm.org/kcdb/)