ICH Q2(R2) & Q14 Guidelines and impact on validation in OMCL Laboratories

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After 18 years from the first implementation, the ICH Q2(R1) guideline needed an update to introduce a lot of new techniques and technologies, previously not in scope.

The decision was finally made and the group started the work in November 2018 to discuss what part of the current guideline to keep, which one to update and what technologies can be included. At the end the decision was made to add all non-linear, multivariate and biological technologies to the scope, which created many difficulties in modifying the text to be inclusive of all. Additionally a rearrangement of the chapters and a clarification of some terminology was performed. The main changes and news present in the Step-2 draft document are presented to the audience. The new guideline should remain current for the next 15-20 years.

The ICH Management Committee additionally decided, to add to the group work-plan, the generation of an additional guideline to support users in the analytical procedure development and to introduce the possibility to expand the development to a PAR/MODR model (also known as aQBD), in order to possibly get more regulatory flexibility.

The impact of these changes to an OMCL Laboratory, which is an ISO/IEC 17025 accredited one and part of the regulator, is also presented.

Correct choice and application of certified reference materials in method validation in food analysis

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Food analysis is the key step to ensuring product quality. It also enables control bodies to implement regulatory requirements correctly, as well as to verify compliance with national and international food standards and nutrition labelling requirements. It is worth to consider the fact that foodstuffs are one of the most common sources of serious illnesses worldwide, ranging from diarrhoea to cancer. An estimated 600 million people fall ill every year due to contaminated food. This underlines the utmost importance of achieving reliable foodstuff analyses. Therefore, accurate, and reproducible analyses are essential. Method validation, including correct sub-sampling, sample preparation, measurement, result evaluation and reporting, which proofs a performance that is fit for the intended purpose, is key to achieving this goal efficiently.

Before validating a method, the following questions about qualitative or quantitative procedures must be examined:

- Qualitative procedures (e.g. detection of prohibited substances) with the question of whether a substance is present in a particular matrix or not (determine the decision limit and check the selectivity and the blank values).
- Quantitative methods, with which substances over a large range of applications can be measured (matrix, measuring range, etc.) are very demanding in their validation.

As a rule, the complete validation of a quantitative method shall include the following criteria: Scope, selectivity/specificity, calibration function, precision, trueness, decision limit, limit of quantification, robustness, and uncertainty of measurement.

Certified reference materials (CRMs) are essential for an in-depth method performance assessment The choice of the correct CRM needs consideration about the matrix, which should be as close as possible to the matrix of the test substance, and the analytes in the defined concentrations. Application of such a certified reference material for method validation, especially for purposes of determining the trueness, limit of quantification and uncertainty of measurement, ensures the comparability and reliability of results delivered by this method. By using an NMI-certified reference material, whose content of analyte is traceable to the SI, you can ensure metrological traceability of your method.

[1] SAS, Leitfaden zur Validierung chemisch-physikalischer Prüfverfahren und zur Abschätzung der Messunsicherheit Dokument Nr. 324.d.
[2] European Accreditation EA-4/14 INF 20023
[3] ISO Guide 32, Calibration in analytical chemistry and use of certified reference materials
[4] ISO Guide 33, Reference materials – Good practice in using reference materials

Non-Target Methods: Challenges and Perspectives

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In recent decades, high resolution mass spectrometry (HRMS) techniques have been found application not only for research purposes but also in routine analysis. These techniques create growth prospects in the field of food authenticity, emerging contaminant control, development of new diagnostic tools in the field of health. Consequently, these perspectives provide the opportunity to discuss issues related to quality assurance of measurements of these methods with the goal of standardization, accreditation, introduction to routine analysis and their integration into regulatory frameworks. Two new approaches are introduced with the HRMS techniques, suspect screening and non-target screening methods. Suspect screening involves searching through a database of known and expected compounds for an unknown sample («known unknowns»). On the contrary, non-target screening involves the identification of chemical compounds without prior information («unknown unknown»), with primary purpose of discovering new indicators for monitoring an analytical problem. Moreover, the combination of suspect and non-target screening offers a complete view of the chemical profile of a sample, an advantage that was not possible using previous approaches. However, the following questions about non-targeted methods need to be addressed: “How is a non-targeted method validated?”

This work presents the problems, need for harmonization these methodologies, as well as the progress made so far about the quality assurance of measurements, the quality characteristics that can be applied as part of ISO 17025 and the existing gaps that need to be filled.

BCR sequential extraction procedure and its application to mine tailings and fly ashes

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Valorisation of industrial waste is a part of the Circular economy strategy of EU. In the RecMine project mine tailings and fly ashes from different sources are studied aimed at their use as raw materials for geopolymers synthesis. For estimation of raw materials as well as the final products, the environmental foot print is planned to be assessed. One step in the assessment is the study of the potential toxicity of heavy metals by testing the mobility of heavy metals, applying different sequential extraction procedures. Additionally, the same procedures are applied to the obtained geopolymers to study the level of heavy metals encapsulation in the geopolymer matrix and correspondingly the environmental footprint of the newly obtained materials. To verify the sequential extraction, the BCR procedure and CRM BCR 701 were chosen. It should be pointed out that the commercially available CRM present soil material that differs from mine tailing and fly ashes. Thus applying the BCR on CRM one can estimate the method behaviour in the laboratory without encountering the specificity of raw materials and geopolymer samples. Moreover, in the research laboratory the chosen equipment is appropriate for the quantity and size of the samples tested which impose to adopt the BCR procedure. However, it could alter the analytical behavior of the standard procedure used for CRM testing [1,2]. In this study the BCR procedure was modified by lowering the weight of the sample but preserving the solid-to-liquid ratio, as well as applying different procedures for supernatant separation. ICP-OES measurement was used for determination of Zn, Pb, Cu, Ni, Cd and Cr in the extracts. Agreement between triplicates was in the frame of 10%. The amount of extracted metals in the sequential procedure (Step 1+Step 2+Step 3+residual) agreed with the certified values. However, some discrepancy in the amount of the analytes in different steps was observed. The BCR procedure and 5-step sequential extraction [3] was applied to study the environmental behavior of potentially toxic elements in industrial samples (mine tailing and coal combustion by-products) from Bulgaria and Romania, as well as geopolymer materials obtained with these precursors.

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[2] R. A. Sutherland, *Analytica Chimica Acta,* **2010**, *680*, 10–20.
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Digital measurement and control technology in the analytical sciences and its quality assurance

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Various types of equipment are used in an analytical process. Until the 1970s, these were operated with knobs and levers. The measurement results were output via moving pointer displays and chart recorders. For adjustment, trimmer potentiometers were adjusted with screwdrivers.
Then the first devices with digital displays appeared. There was great confidence in the values displayed. Buttons and switches were replaced by keyboards. Data could be stored and retrieved. Everything seemed to be in order.
Doubts arose here and there. Reintegration did not give the same result as the original integration. The signal on the digital integrator was less high than on the analogue recorder. What was going on?
Computerised systems were newly used for further evaluation of measurements and statistics.
The pharmaceutical world was shocked with CFR 21 Part 11.
Then after 31 December 1999 came 1 January 2000. Equipment that managed a date got into trouble. We learned the terms firmware and data formats.

How could we regain confidence in our data and keep it permanently?

In the regulated laboratory, equipment qualification and IT qualification and validation became standard. So everything is under control, right?

The control of data in general has been massively expanded with the term data integrity.

Data protection became an issue and took on a new dimension with the cloud.

The challenge continues...

Ion mobility as additional Metrological Value – the Invaluable Benefit of another Dimension in Hybrid Mass Spectrometry

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The use of LC (and GC) in combination with ion mobility high resolution mass spectrometry for small molecule analysis has increased across multiple areas of research including food safety, food characterization, natural products, as well as extractable and leachables analysis.

Utilising ion mobility to determine the specific measurement of the rotational size of an ionized molecule in nitrogen gas has several benefits for the future of analytical methodologies. The measurement is reproducible and intrinsic to molecular structure. Ion mobility also provides an additional separation dimension complimentary to chromatographic separation and mass separation, which facilitates the understanding and formation of characteristic fragments in MS2 techniques.

The size of a molecular ion (in nitrogen gas) is determined by its collisional cross section (CCS) and measured in Å2 (10-20m2). It is independent of ion mobility platform or chromatographic technique. For non-targeted screening assays ion mobility CCS values provide an additional identification point to reduce false detection rates, in combination with conventional retention times, precursor ion and product ions. The CCS value can be generated through experimental values produced using certified reference materials (<2%), or through theoretical calculations, (<5%) or from known analytes in previously characterised samples.

Long term and cross platform CCS reproducibility will be presented. Increased assay retention time flexibility, enhanced specificity, and enhanced peak capacity that can be attained when integrating ion mobility with LCMS analysis. Retrospective CCS non-targeted screening further illustrates the utility of a CCS descriptor, in addition to facilitating differentiation of isomeric species.

Need for the validation of on-site test kits, portable devices and continuous measuring devices for water quality monitoring

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On site test kits (e.g., immunoassays, such as ELISA), portable devices (e.g. sensors, lab-on-chip systems, flow cytometers), and continuous measuring devices (e.g. in situ sensors, on-line instruments) can measure and monitor physico-chemical parameters such as nutrients, organic matter, single or multiple inorganic metals and organic compounds (e.g. examples: pesticides, biocides, pharmaceuticals, industry chemicals), microbiological parameters (presence of bacteria/viruses) or toxicity and ecotoxicity. Moreover, some of the water quality parameters to be monitored can be defined by their method, meaning that any significant change in the method will engender a different measurand.

These devices are foreseen be very useful to improve water quality assessment under EU directives (e.g. Water Framework Directive, Drinking Water Directive, Urban Waste Water Directive) as well as for monitoring industrial processes to minimize their operating cost and their environmental footprint leading to higher quality effluents.

Although these devices have clear advantages (e.g. fast response; real-time monitoring), they are perceived as less reliable than conventional methods. Their innovative nature and/or operation mode require specific validation strategies that differ significantly from conventional analytical methods.

A harmonised framework to validate these devices will improve their overall acceptance and promote their use more widely. The different measuring principles and continuous operation mode require developing specific performance assessment infrastructure demonstrating they are fit for the intended use during the product's life cycle and the most demanding operating conditions.

Laboratory medicine – mandatory quality controls are self-evident

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Laboratory Medicine consists of different disciplines looking at different aspects of the human body: clinical chemistry, haematology, immunology and microbiology.

Each day a huge number of samples are analysed from persons being healthy and patients being extremely sick. The variety of analytical methods applied is enormous including e.g. fully automated photometric assays, cell counting, microscopy, HPLC, LC-MS/MS, ICP-MS, bacterial cultures.

The laboratory usually receives only tubes with blood, urine or another body fluid and does know neither the patients disease nor his actual clinical symptoms. The physicians in contrast select their therapeutic approach using laboratory results in > 60% of cases. This implements a very high quality of the results independent of their size and personal structure of the medical laboratory.

Due to the importance of a high quality of the results of the medical laboratories, a high number of countries all over the world have edited guidelines concerning the internal and external quality controls in the medical laboratory. In many countries, these guidelines often have a standing of a legal document.

In Switzerland, internal quality controls are mandatory for all analytes and the frequency of the measurement of these samples varies from “one control sample every50 samples” to “every two weeks” depending on the type of method, which is applied. The appraisal of the results is exactly described and the storage of the results well defined. There is a long list of analytes for which also external quality controls have to be performed mostly ≥ 4 times per year. There are commercial centres present in many countries sending out external quality control samples all over the world. In most countries, they need an accreditation according to ISO/IEC 17043.

In medical laboratories usually a lot of money is spent for this internal and external quality control samples and the also are an additional workload for the personnel. Nevertheless nobody has any doubt that they are of immense use for the daily work. The internal quality control samples are the only samples in the laboratory where we know the results. They give us the confidence that the >10’000 results which we produce in our laboratory every day are correct and add to the correct treatment of the patient.

The Proficiency Testing System of the Organisation for the Prohibition of Chemical Weapons

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The Organisation for the Prohibition of Chemical Weapons (OPCW) maintains a network of Designated Laboratories to perform off-site analysis of suspect samples in support of the OPCW to monitor compliance with the Chemical Weapons Convention (CWC). In order to obtain and maintain OPCW designation, a laboratory must establish a quality system, maintain a valid accreditation by an internationally recognised accreditation body for the scope it is seeking designation, and must successfully participate in the proficiency testing (PT) programme of the OPCW. In a PT, a laboratory must analyse two sets of three samples within 15 calendar days for the presence of an almost unlimited number of chemical warfare agents and their related compounds. At the end of the test period, the laboratory must submit a report that meets most stringent reporting criteria and maintain a chain of evidence throughout the report.

The presentation aims to show how OPCW PTs are organized and what criteria the participating laboratories must meet to successfully pass the test. Additionally, it will highlight challenges that may arise when analysing samples for the presence of chemical warfare agents and their related compounds. As an example, the presentation will show how the Analytical Chemistry Group of Spiez Laboratory, one of the Designated Laboratories of the OPCW for the analysis of authentic environmental samples, meets that challenge.

Ensuring Validity of Examination Results: What is new in the new ISO 15189

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The new edition of the ISO 15189 [1] has been available to medical laboratories since December 2022; a transition period of three years is considered to be adequate for both laboratories and accreditation bodies to shift smoothly to the new edition, addressing all new or adjusted requirements. In this presentation, the main changes in ISO 15189:2022 towards ensuring validity and accuracy of examination results in medical laboratories compared with the 2012 version are discussed. A main change refers to the structure which is now aligned with ISO/IEC 17025 [2,3] and recent editions of other standards in the ISO 17000 series. Further to this, it is noted that requirements for medical laboratories to plan and implement actions addressing risk and opportunities are introduced in the new standard. This is part of the overall philosophy of the standard and is reflected in all clauses, including those dealing with the pre-examination, the examination and the post-examination processes. Great emphasis is given to sampling and the pre-examination process with reference to supporting standards e.g. ISO 20658 [4]. Contrary to ISO/IEC 17025, uncertainty arising from sampling is not referred to; this seems to be related to inherent difficulties for such an evaluation [5]. Requirements for equipment calibration and metrological traceability of measurement results are more detailed; similarly, the specific clause on ensuring the validity of examination results, specifying requirements for the internal quality control (IQC) and the external quality assessment (EQA), is also more detailed. Reference is made to some additional supporting standards, namely ISO 17511 [6], ISO 17034 [7] and others.

[1] ISO 15189:2022, Medical laboratories - Requirements for quality and competence
[2] ISO 17025:2017, General requirements for the competence of testing and calibration laboratories
[3] A new ISO/IEC 17025 for laboratories, https://www.eurachem.org/index.php/publications/leaflets/iso-iec-17025-2017
[4] ISO/FDIS 20658, Requirements for the collection and transport of samples for medical laboratory examinations
[5] K. Tsimillis, S. Michael, Uncertainty From Sampling: Could the Requirements of ISO/IEC 17025 (2017) Be Adopted in Medical Laboratories? *IJRQEH*, **2022**, 11(1), 1-8, DOI: 10.4018/IJRQEH.295082
[6] ISO 17511:2020, In vitro diagnostic medical services – Requirements for establishing metrological traceability of values assigned to calibrators, trueness control materials and human samples
[7] ISO 17034:2016, General requirements for the competence of reference materials producers

Comparison of standardized and novel methods for oil spill source identification in real spill scenarios reproduced in proficiency tests

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The assessment of oil patterns equivalence of spill (Sp) and suspected source (SS) samples is based on the comparison of ratios between GC-MS signals of oil discriminating compounds, i.e., diagnostic ratios (DR). The Student's t statistics (S-t) and a maximum relative difference (SC), proposed by Nordtest [1] and EN 15522-2 [2] reference methods, respectively, have been used for DR comparison, even though they are based on false DR normality assumption or on a maximum DR dispersion. A novel approach based on the accurate Monte Carlo Method (MCM) simulation of DR probability distribution was developed and experimentally validated from the analysis of unweathered oil patterns [3, 4]. The present study describes the comparison of the application of MCM, S-t and SC approaches to assess real spills of different oil products reproduced in three International Round Robin Tests (RR). It is quantified and compared the probability of each approach correctly concluding about oil pattern equivalence from one (δ) or two (ω) sets of replicate GC-MS signals and the number of DR mismatches from the spill and oil different from the spill source. The MCM approach based on two independent DR comparison trials was the only one consistently producing oil fingerprint comparisons with a ω above the minimum value of 98%. MCM also performed better in identifying differences between the Sp and a non-matching SS. The assessment of δ variation with the number of compared DR allowed concluding that analysis quality does not improve significantly if more than 22 DR are considered. The complexity of the MCM approach is overcome by using user-friendly and validated software.

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Measurement uncertainty from sampling and its roll in validation of measurement procedures

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It is now widely accepted that the measurement process usually begins when the primary sample is taken. The uncertainty of measurement (MU) must therefore include contributions that arise from the sampling, and also any physical preparation of the sample that often occurs before the sample reaches the laboratory. Guidance on how to estimate MU so that it includes sampling (UfS) [1] has been widely applied to a wide range of application sectors (e.g. food, feed, water, sediment, soil, gases).

Recent revision of ISO/IEC 17025 [2] has recognised the inclusion of sampling within the measurement process. This has implication for the Validation of Measurement Procedures that Includes Sampling (VaMPIS). Eurachem has therefore set up a Joint Task Group to produce Supplementary Guidance (SG) on how to achieve VaMPIS.

The uncertainty of the measurement value (MU) is a key parameter that summarises the effects of all of the other parameters of the analytical method that are usually considered during validation. It has the further advantage that it can be used to integrate sampling (and physical sample preparation) into the whole measurement procedure. There will be an explanation of how MU (that includes UfS) can be estimated, and then how it can be used as the key parameter to judge the fitness-for-purpose (FFP) of the whole measurement procedure during its validation. Examples will be used to show how this approach can be applied to VaMPIS for all measurement procedures, whether they are performed *ex situ* (sample removed for lab analysis) or *in situ* (no sample removed).

[1] Ramsey M.H., Ellison S. L. R., and Rostron P.(eds.) (2019) Eurachem/EUROLAB/ CITAC/Nordtest/ AMC Guide: *Measurement uncertainty arising from sampling: a guide to methods and approach*, Second Edition, Eurachem, ISBN 978-0-948926-35-8 http://www.eurachem.org/index.php/publications/guides/musamp
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The Importance of Traceability or how to Achieve Comparability of Chemical Measurements

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Metrology traceability refers to the ability to trace the measurement results of an instrument or system ultimately back to the SI unit (*Système international d'unités*) and is a critical aspect of ensuring the accuracy and reliability of measurement data in several testing fields such as manufacturing, healthcare, and environmental monitoring. Together with measurement uncertainty, metrology traceability is an important factor for a laboratory to meet the requirements of the new ISO/IEC 17025:2017 standard.

Traceability provides a means of establishing confidence in measurement results by enabling comparison and validation of measurements made by different instruments or laboratories. It also ensures that measurements are consistent over time and across different locations.

It is typically achieved through a chain of comparisons, where the calibration of an instrument is compared against higher-level standards until a traceable reference is reached. Selection of the proper reference material in the analytical workflow and evaluation of its suitability in the specific testing application are critical considerations for the laboratory.

Analytical methods accredited under the ISO/IEC 17025 and ISO 17034 scope enable the realization certified reference materials with highest metrological accuracy and precision.

This presentation will cover the above-mentioned areas along with a discussion of the importance for maintaining traceability and reporting of uncertainty through selection of the proper reference material grade. Testing examples will be provided to illustrate the importance of proper selection criteria, storage & handling requirements, and intended use of reference materials in analytical testing applications.

Measurement uncertainty evaluation with numerical methods

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The basic rules for combining measurement uncertainties from different sources are well known. For example, when two independent input quantities are added, their uncertainties can be combined directly by squaring the standard uncertainties, adding the squares and taking the square root of the resulting sum. For simple multiplicative expressions, the same can be done with relative standard uncertainties.

There are, however, many circumstances in which these simple rules are inadequate. The first is when the expression for calculating the measurement result is not a simple multiplicative or additive expression. Then, we should either proceed by reducing the expression to a series of simpler expressions for which the basic rules do apply – a process that is specific to each different expression – or we should apply a more general formula. The general first-order expression for a combined standard uncertainty u_c in the GUM [1] is

$$u_c = \sqrt{\sum_i^n \left(\frac{\partial y}{\partial x_i}\right)^2 u(x_i)^2} \qquad (1)$$

Although partial derivatives are covered in most science degree courses, the process is again specific to the particular expression; it is also quite prone to mistakes in algebra and invariably takes time to do manually.

A further difficulty arises when the effect of a particular input quantity on the result cannot be safely reduced to a simple linear expression – that is, we have serious non-linearity. Neither the basic rules, nor formula (1), then apply, and formula (1) needs extension to include higher-order partial derivatives [1].

This presentation will provide an overview of numerical approaches to measurement uncertainty evaluation. These approaches can greatly simplify measurement uncertainty evaluation by applying relatively simple and very general computational methods that only require the formula used to calculate the measurement result. The discussion will include the use of "finite-difference" approaches that can be implemented easily in a spreadsheet [2, 3], and will also cover the use of Monte Carlo simulation methods as proposed in supplement 1 to the GUM [4]. MCS can, again, be implemented using a spreadsheet [3]. Simple examples will be included to illustrate the approaches. A brief example of the application of Bayesian methods will also be provided.

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The impact of input data on the evaluation of the measurement uncertainty: A case study

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The measurement uncertainty reported on results from the determination of a specific measurand depends on the considered input data and on how the information is used [1,2,3]. The reported uncertainty must be smaller than the agreed target or maximum admissible uncertainty [4]. This communication presents and compares three examples of the top-down evaluation of the uncertainty of the determination of total As in marine sediments where precision and analyte recovery components were calculated from different input data as specified in the following table [2,3,5].

Example	Precision uncertainty	Mean analyte recovery uncertainty
A1	Analysis of three real sediment samples on different days	Analysis of a Certified Reference Material, CRM
A2	Analysis of three real sediment samples on different days	Analysis of a CRM and two spiked samples with native analyte
A3	Analysis of digested solution on different days and duplicate analysis of 30 real sediment samples	Single analysis of samples from 22 proficiency tests

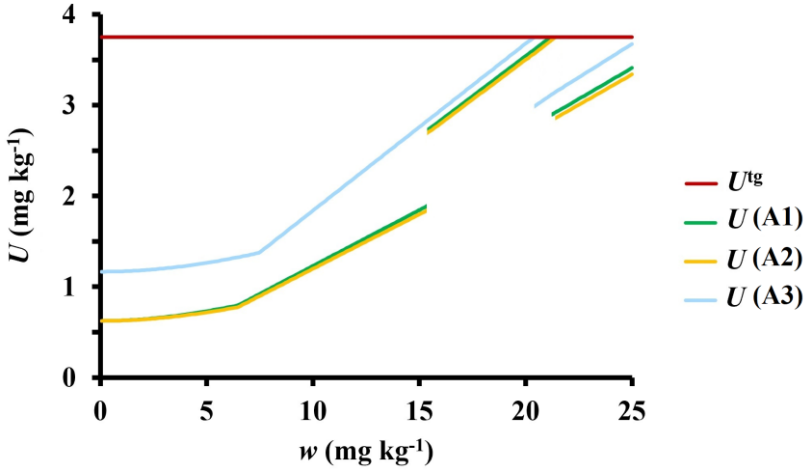

Figure. Models of measurement, U, and target, U^{tg}, expanded uncertainties, for 95% confidence level, for the measured total As mass fraction of sediments where precision and mean analyte recovery are assessed from different performance data. For larger mass fractions, duplicate sample analysis is required.

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