Another top down MU method – ISO 11352 made simple

1.0 Introduction

There are several methods for estimating measurement uncertainty (MU) by the holistic top down approaches, which study MU from the viewpoint of the whole test method performance. We have discussed the use of ISO 21748:2010: *Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation* which employs the reproducibility of the test method from proficiency testing (PT) program(s) as one of the main uncertainty components in the combined standard uncertainty after confirming the method repeatability meets the criteria set and the method bias (trueness) has been evaluated to be satisfactory.

2.0 The ISO 11352:2012

An alternative method ISO 11352:2012: *Water quality – Estimation of measurement uncertainty based on validation and quality control data* recommends another avenue in estimating measurement uncertainty in chemical analysis, by statistically taking a combination of **precision estimate** (such as intermediate precision), and the **method and laboratory bias** into one uncertainty measure. This approach has removed the difficulty in conducting suitable inter-laboratory comparison (ILC) studies or finding a proficiency testing (PT) program provider for a newly developed test method. Instead, the data from own method validation and analytical quality control protocols are utilized here.

Many terms have been used to describe the precision data through repeated analysis on a stable laboratory control sample (LCS) over a period of time by different analysts and/or different equipment and reagents ***within*** a laboratory. They are known as intermediate precision, intermediate reproducibility, within-laboratory precision, within-laboratory reproducibility, *etc*.

This international standard advocates that if the measurement result originates from a controlled analytical process, it is then not necessary to estimate the MU of each individual measurement result. That means the estimation of MU should apply to all of the measurement results under controlled conditions with a quality assurance program, independently of, say, sample matrix and analyst.

It further suggests that if the MU varies significantly, depending on sample matrix and/or concentration range, the uncertainty estimation shall be made separately for each matrix and/or concentration range.

Also, the analytical data obtained must be completely random and fall within the normal probability distribution. The Anderson Darling statistic or other suitable tests for data normality is used to confirm that this important assumption is valid.

3.0 The uncertainty components to be considered

In short, for this international standard, we only need to consider two main aspects of uncertainty contributors for a specific analytical method under same controlled conditions as used when a routine analysis is carried out, coupled with a robust quality assurance program, namely:

- intermediate precision estimate from validation process
- method and laboratory bias data estimate

3.1 Intermediate precision (within-lab reproducibility) standard uncertainty, $u_{R'}$

a) Use of quality control samples covering the whole analytical process

When the matrix and concentration range of a laboratory control sample (LCS) are similar to those of the routine samples for analysis, the intermediate precision standard deviation $s_{R'}$ is equal to the intermediate precision standard uncertainty $u_{R'}$, i.e.

$$u_{R'} = s_{R'} \qquad [1]$$

b) Using synthetic standard solutions as quality control samples

If LCS with an identical matrix to test samples are not available, a laboratory prepared synthetic standard solution can be used, which may have a matrix which differs from that of routine samples.

Apart from subjecting this standard solution to the whole analytical process to obtain the intermediate precision standard uncertainty, we need to consider an additional uncertainty component due to possible increase inhomogeneity of the analyte in the matrix.

This additional uncertainty as a within-laboratory repeatability component, u_{Range} can be estimated from a series of duplicate analyses of the actual test samples over a range of concentrations.

For example, if, in a hypothetical experiment, we have a duplicate set of analytical data 10.8mg/L, and 11.3mg/L, the difference between the duplicate, D = 11.3 – 10.8 or 0.5mg/L and the mean result = 11.05mg/L.

The relative range standard uncertainty expressed as % relative standard deviation, R_{rel} therefore equals to (0.5 x 100)/11.05 or 4.52.

Table 1 below shows 10 sets of duplicates on 10 test samples with different concentrations, and their respective relative range standard deviations, $R_{i,rel}$.

The last column calculated the mean $\overline{R}_{rel}$ of the 10 range values obtained.

Table 1: Evaluation of 10 duplicated analyses on different test samples of varied concentrations in mg/L.

n	1	2	3	4	5	6	7	8	9	10	$\overline{R}_{rel}$
x_1	10.8	15.6	7.5	12.1	8.9	9.7	14.2	10.3	10.8	15.6	
x_2	11.3	15.2	7.7	11.6	9.4	9.3	13.8	10.7	11.1	15.2	
$R_{i,rel}$	4.52	2.6	2.63	4.22	5.46	4.21	2.86	3.81	2.74	2.6	3.57

Then, the following equation [2] is used to estimate the intermediate precision based on the repeatability uncertainty of the synthetic standard solution and the uncertainty of testing different test samples with variable concentrations:

$$u_{R'} = \sqrt{u^2_{R'(s\tan d)} + u^2_{r(range)}} \qquad [2]$$

where,

$u_{R'(s\tan d)}$ is the standard uncertainty of the synthetic standard solution

$u_{r(range)}$ is the standard uncertainty of the range control which is:

$u_{r(range)} = \dfrac{\overline{R}_{rel}}{1.128}$ where $\overline{R}_{rel}$ is the mean range of the duplicated analyses.

c) Unstable control sample

Where stable control samples are not available, the ISO standard suggests to consider two uncertainty components:

- the repeatability from the calculation of the mean of the ranges of duplicate analyses, i.e. $u_{r(range)}$
- the variation resulted from the means of different batches of analyses, i.e. $u_{R'(batch)}$; in many cases, this component relies on scientific judgment based on the analyst's experience

The equation [3] is then used for the within-lab reproducibility, $u_{R'}$:

$$u_{R'} = \sqrt{u^2_{r(range)} + u^2_{R'(batch)}} \qquad [3]$$

3.2 Method and laboratory bias, u_b

Generally speaking, sources for biased results should be investigated and eliminated during the method validation or verification process. But an observed bias does often exist for different matrices and different concentrations.

To evaluate the uncertainty associated with method and laboratory bias, two components are to be estimated:

i. the test result bias itself, expressed as the difference between the test result and the nominal, certified or accepted reference value;
ii. the uncertainty of the nominal or certified reference value

Note 1: the bias uncertainty component can be neglected if $u_b < u_{R'}/3$.

a) Analysis of suitable reference materials

The following equations [4] and [5] are used for uncertainty component associated with method and laboratory bias:

i. For n_r number of certified reference materials (CRM's) studied:

$$u_b = \sqrt{\frac{\sum b_i^2}{n_r} + \bar{u}^2_{Cref}} \qquad [4]$$

ii. If only one reference material is available, the repeated results of analyses of this reference material are treated as the best available estimate for the measurement uncertainty component associated with method and laboratory bias, u_b.

So, when only one CRM is used, the bias uncertainty component is:

$$u_b = \sqrt{b^2 + \frac{s_b^{\,2}}{n_M} + \overline{u}^{\,2}_{Cref}} \qquad [5]$$

where:

b_i is the i^{th} bias which is the difference between the mean measured value and the accepted reference value (ARV) of the i^{th} reference material

b is the difference between the mean measured value and the accepted reference value of the single CRM

n_r is the number of CRM's

n_M is the number of bias measurements on the reference material

$\overline{u}_{Cref}$ is the mean value of all u_{Cref}, which are the estimated standard uncertainties of the CRM's given

s_b is the standard deviation of the measured values of the reference material

b. The use of PT or inter-laboratory comparison (ILC) results

Results from PT programs or inter-laboratory comparisons may be used in the same way from analysis of reference materials, if the assigned value in the inter-laboratory comparison is a sufficiently good estimate of the true value. An important condition to note is that the laboratory's participation in such studies must be satisfactory (i.e. not being labelled as outlier with z-score amongst the participants being less than 2 for 95% confidence). Alternatively, the Mandel's h & k statistic test can be applied to confirm this assumption.

The differences, D_i between the test results and the assigned values of the different samples are calculated and squared before making an estimate of root mean square of the differences, D_{rms}:

$$D_{rms} = \sqrt{\frac{\sum D_i^{\,2}}{n_{ilc}}} \qquad [6]$$

where,

n_{ilc} is the number of inter-laboratory comparison samples analyzed

Note 2: If the individual differences and the uncertainties of the assigned values vary significantly, it may be necessary to separately estimate uncertainties for the different cases.

The mean uncertainty of the assigned values of the inter-laboratory comparison samples can be calculated as (a) median or robust mean, or (b) arithmetic mean from the results of the participating laboratories (i.e. consensus value), $\bar{u}_{Cref}$ as follows:

$$\bar{u}_{Cref} = \frac{\sum u_{Cref,i}}{n_{ilc}} \quad [7]$$

where,

if the **median** or **robust mean** is used as consensus value:

$$u_{Cref,i} = 1.25 \times \frac{s_{R,i}}{\sqrt{L_i}} \quad [8]$$

or,

if the **arithmetic mean** is used as consensus value:

$$u_{Cref,i} = \frac{s_{R,i}}{\sqrt{L_i}} \quad [9]$$

where,

$u_{Cref,i}$ is the uncertainty of the assigned value of the inter-laboratory sample i;

$s_{R,i}$ is reproducibility standard deviation from the inter-laboratory comparison for sample i;

L_i is the number of participating laboratories for sample i

Finally, the standard uncertainty component associated with method and laboratory bias, u_b, is calculated as in equation [10]:

$$u_b = \sqrt{D^2_{rms} + \bar{u}_{Cref}} \quad [10]$$

Where,

D_{rms} is the root mean square of the differences

$\bar{u}_{Cref}$ is the mean uncertainty of the assigned values of the inter-laboratory comparison or PT samples

c. Making use of the discovery experiments

A recovery experiment checks for the recovery of a known amount of analyte added to a previously analyzed sample. Such experiment can also be used to evaluate bias. To be statistical relevance, this recovery experiment should be performed with at least six different samples of the relevant matrix.

In this case, the uncertainty components associated with method and method bias, u_b are:

- the difference between observed and known concentration of the analyte
- the uncertainty in the concentration of the analyte added to the test sample

The standard uncertainty associated with method and laboratory bias, u_b, estimated from recovery experiments is:

$$u_b = \sqrt{b^2{}_{rms} + u^2{}_{add}} \qquad [11]$$

where

u_{add} is the uncertainty in the concentration of the analyte added, which should cover two uncertainty components, i.e. the volume made up and the amount of analyte added;

b_{rms} is the root mean square of the deviations from the recovery experiments, which is calculated from the equation below:

$$b_{rms} = \sqrt{\frac{\sum b_i^2}{n_{\mathrm{Re}c}}} \qquad [12]$$

where

b_i is the deviation from the 100% recovery of the i^{th} recovery experiment or from the mean recovery, if the results are corrected with this mean recovery;

n_{Rec} is the number of recovery experiments

4.0 Calculation of the combined standard uncertainty and expanded uncertainty

Under 95% confidence limit, the combined standard uncertainty, u_c, for $u_{R'}$ and u_b, and expanded uncertainty, U, can be calculated by the following equations:

$$U = 2u_c = 2\sqrt{u^2{}_{R'} + u^2{}_b} \qquad [13]$$

$$U_{rel} = 2u_c{}_{,rel} = 2\sqrt{u^2{}_{R',rel} + u^2{}_{b,rel}} \qquad [14]$$

where,

$u_{R',rel}$ and $u_{b,rel}$ are the relative standard deviation of $u_{R'}$ and u_b, respectively

5.0 Conclusion

It is obvious that the holistic top down approach in MU evaluation is relatively simpler than using the GUM (so called bottom up) method which considers all uncertainty components in each of the analysis steps of the test method. This top down approach makes use of the readily available method validation data and outcomes from PT or ILC studies participated. Another advantage is that the MU estimate by this manner is dynamic and current as the quality control data are being updated regularly.