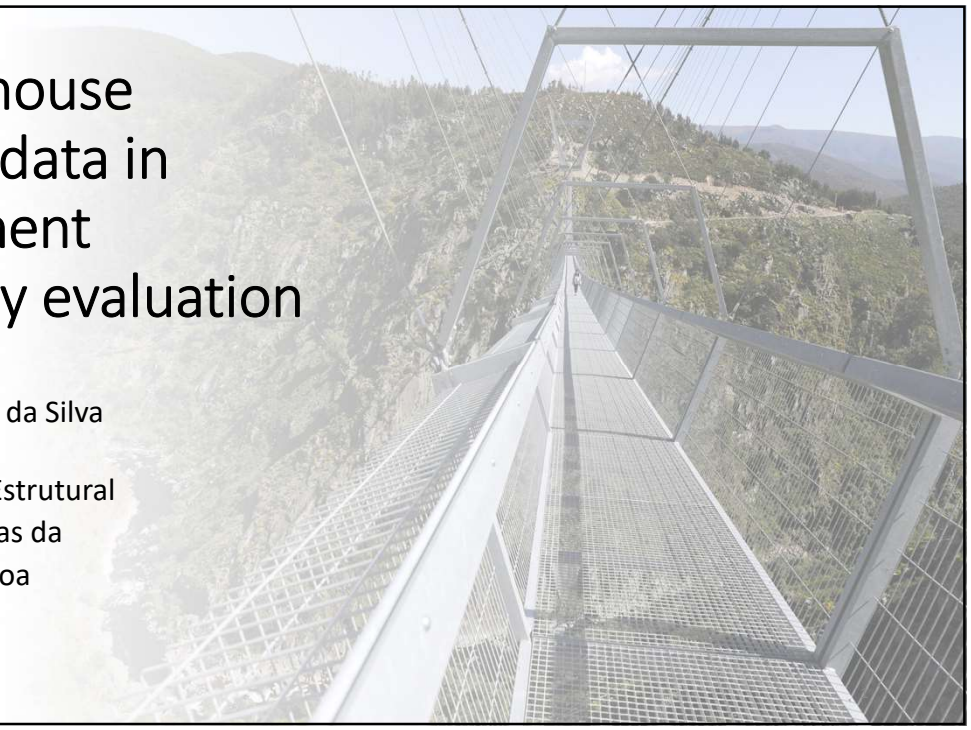
Use of in-house validation data in measurement uncertainty evaluation



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Outline

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Modelling precision with the concentration
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Introduction

Top-down uncertainty evaluations are very popular due to the simplicity and the fact that the simplification does not terribly overestimate measurement uncertainty (MU).

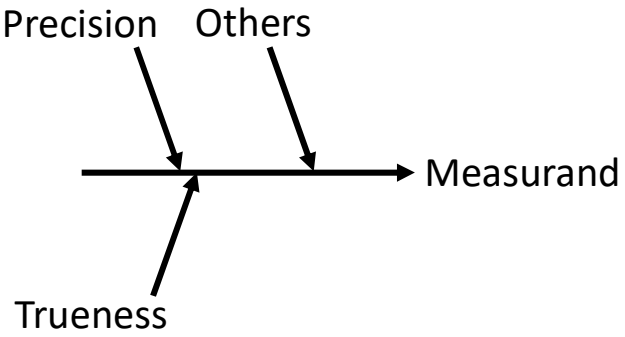
Introduction

However, some challenges have to be faced to improve the reliability and efficiency of MU evaluation:

- How to model uncertainty in a wide concentration range
- How to use all reference materials in trueness assessment
- How to handle bias
- How to adapt MU evaluation to regulated validation design

Top-down uncertainty components

Three uncertainty components should be quantified and combined:



SLR Ellison, VJ Barwick, Accred. Qual. Assur. 3 (1998) 101.
A Maroto, J Riu, R Boqué, FV Rius, Anal. Chim. Acta 391 (1999) 173.
B Jülicher, P Gowik, S Uhlig, Analyst 124 (1999) 537.

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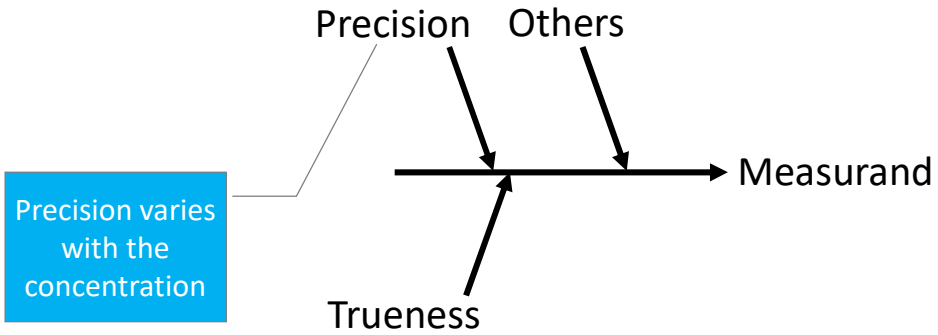
Top-down uncertainty components

Three uncertainty components should be quantified and combined:



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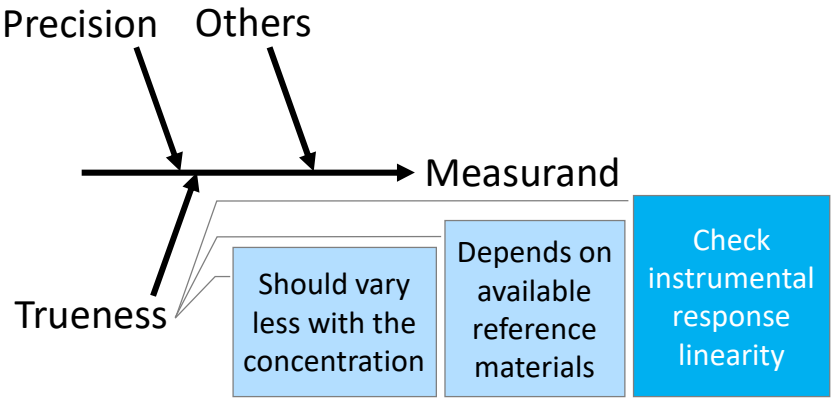
Top-down uncertainty components

Three uncertainty components should be quantified and combined:



Modelling precision with the concentration

It is known that:

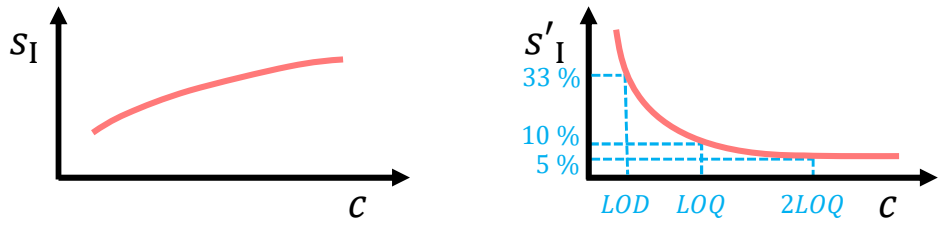
LOQ → C.V. = 10 %
LQD → C.V. = 33 %

(these limits should be estimated under intermediate precision conditions)

LOQ - Limit of quantification
C.V. – Coefficient of variance
LOD – Limit of detection

Modelling precision with the concentration

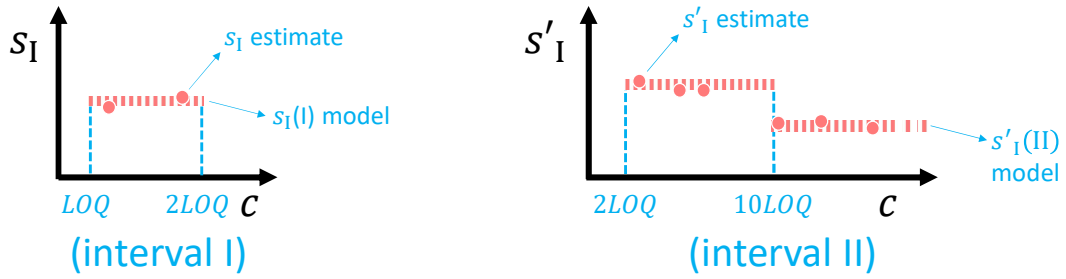
It is known that:



s_I - intermediate precision standard deviation
s'_I - intermediate precision RELATIVE standard deviation (s_I/c)

Eurachem/CITAC Guide: Setting and Using Target Uncertainty in Chemical Measurement, Eurachem, 2015

Modelling precision with the concentration



s_I - intermediate precision standard deviation
s'_I - intermediate precision RELATIVE standard deviation (s_I/c)

Trueness evaluation

If *N* Certified Reference Materials, proficiency test samples and spiked samples without native analyte are analysed:

overall mean recovery

$$\bar{\bar{R}} = \sum_{i=1}^{N} \bar{R}_i \Big/ N$$

i^{th} mean recovery

recovery variance (interm. pres.)

trueness standard uncertainty

$$u_{\mathrm{T}} = \frac{\sqrt{\sum_{i=1}^{N} \left\{ \bar{R}_i^2 \left[\frac{s_{\mathrm{I}}^2(R_i)}{\bar{R}_i^2 \cdot n_i} + \frac{u^2\left(c_{\mathrm{Ref}(i)}\right)}{c_{\mathrm{Ref}(i)}^2} \right] \right\}}}{N}$$

square of the relative standard uncertainty of the i^{th} reference value

number of i^{th} recovery tests

R. Cordeiro, et al., Accred. Qual. Assur. 23 (2018) 57-71.

Trueness evaluation

If *N* Certified Reference Materials, proficiency test samples and spiked samples without native analyte are analysed.
If recovery varies significantly with the studied reference materials.

$$u_{\mathrm{T}} = \frac{\sqrt{\sum_{i=1}^{N} \left\{ \bar{R}_i^2 \left[\frac{s_{\mathrm{I}}^2(R_i)}{\bar{R}_i^2 \cdot n_i} + \frac{u^2\left(c_{\mathrm{Ref}(i)}\right)}{c_{\mathrm{Ref}(i)}^2} \right] \right\} + N^2 s_{\mathrm{I}}^2(\bar{R}_i)}}{N}$$

$s_{\mathrm{I}}^2(\bar{R}_i)$ - variance of the mean recovery.

VJ Barwick, SLR Ellison, VAM project 3.2.1—part (d): protocol for uncertainty evaluation from validation data, LGC, 2000.

Trueness evaluation

After quantifying the trueness uncertainty, it is necessary to assess if the mean recovery is metrologically equivalent to the ideal value of 100%.

$$\frac{\left|1-\bar{\bar{R}}\right|}{u_{\mathrm{T}}} \leq 2$$

True: Results do not need recovery correction that will be assumed as equal to 1

False: Results should be corrected for observed recovery by multiplying by ($1/\bar{\bar{R}}$)

VJ Barwick, SLR Ellison, VAM project 3.2.1—part (d): protocol for uncertainty evaluation from validation data, LGC, 2000.

Combination and expansion of the uncertainty

Optimal approach:

[LOD, 2LOQ[$\rightarrow$ $U = k\sqrt{s_{\mathrm{I}}^2(\mathrm{I}) + \left(\frac{c_{\mathrm{S}} \cdot u_{\mathrm{T}}}{\bar{\bar{R}}}\right)^2}$

c_{S}: sample concentration corrected or not corrected for recovery

$\bar{\bar{R}}$: equal to 1 or $\bar{\bar{R}}$ if $\bar{\bar{R}}$ is equivalent or different from 1

[2LOQ, c_{Max}[$\rightarrow$ $U = k c_{\mathrm{S}}\sqrt{s_{\mathrm{I}}'^2(\mathrm{II}) + \left(\frac{u_{\mathrm{T}}}{\bar{\bar{R}}}\right)^2}$

$s_{\mathrm{I}}'^2(\mathrm{II})$: square of the relative standard deviation at interval II

R. Cordeiro, et al., Accred. Qual. Assur. 23 (2018) 57-71.
C. Palma et al., Talanta 192 (2019) 278-287

Combination and expansion of the uncertainty

Example: Determination of total Cr in sediments
Units: mg kg^{-1}; *U* for 95 % confidence

[1.5, 10[→ $U = 2\sqrt{0.633^2 + \left(\frac{c_S \cdot 0.0189}{1.08}\right)^2}$ value corrected for recovery

[10, 327[→ $U = 2c_S\sqrt{0.0633^2 + \left(\frac{0.0189}{1.08}\right)^2}$

C. Palma et al., Talanta 192 (2019) 278-287

Combination and expansion of the uncertainty

Example: Determination of total Cr in sediments
Units: mg kg^{-1}; *U* for 95 % confidence

[1.5, 10[→ $U = 2\sqrt{0.633^2 + \left(\frac{10 \cdot 0.0189}{1.08}\right)^2} = 1.3\ \text{mg kg}^{-1}$

[10, 327[→ $U = 2 \cdot 100\sqrt{0.0633^2 + \left(\frac{0.0189}{1.08}\right)^2} = 13\ \text{mg kg}^{-1}$

C. Palma et al., Talanta 192 (2019) 278-287

Trueness evaluation based on root-mean-square

Nordtest published a guide that suggests an alternative way of quantifying the trueness uncertainty that avoids the previously described t-test to decide the need for recovery correction.

» Can overestimate the measurement uncertainty

Nordtest, Handbook for calculation of measurement uncertainty in environmental laboratories, NT TR 537 (Ed.4), 2017.
ISO 11352, Estimation of measurement uncertainty based on validation and quality control data, 2012.

Trueness evaluation based on root-mean-square

If *N* reference materials were analysed:

$$u_{\mathrm{T}} = \bar{\bar{R}}\sqrt{\frac{\sum_{i=1}^{N}(\bar{R}_i - 1)^2}{N} + \frac{\sum_{i=1}^{N}\left(\frac{u\left(c_{\mathrm{Ref}(i)}\right)}{c_{\mathrm{Ref}(i)}}\right)^2}{N}}$$

Root-mean-square of relative errors (RMS)

Nordtest, Handbook for calculation of measurement uncertainty in environmental laboratories, NT TR 537 (Ed.4), 2017.
ISO 11352, Estimation of measurement uncertainty based on validation and quality control data, 2012.

Trueness evaluation based on root-mean-square

Combination and expansion of uncertainty components

Optimal approach:

sample concentration not corrected for recovery

[LOD, 2LOQ[→ $U = k\sqrt{s_{\mathrm{I}}^2(\mathrm{I}) + \left(\frac{c_{\mathrm{S}} \cdot u_{\mathrm{T}}}{\bar{\bar{R}}}\right)^2}$

[2LOQ, c_{Max}[→ $U = k c_{\mathrm{S}} \sqrt{s_{\mathrm{I}}'^2(\mathrm{II}) + \left(\frac{u_{\mathrm{T}}}{\bar{\bar{R}}}\right)^2}$

C. Palma et al., Talanta 192 (2019) 278-287

Trueness evaluation based on root-mean-square

Example: Determination of total Cr in sediments

Units: mg kg^{-1}; *U* for 95 % confidence

value NOT corrected for recovery

[1.5, 10[→ $U = 2\sqrt{0.633^2 + (c_{\mathrm{S}} \cdot 0.0450)^2}$

[10, 327[→ $U = 2c_{\mathrm{S}}\sqrt{0.0633^2 + 0.0450^2}$

C. Palma et al., Talanta 192 (2019) 278-287

Trueness evaluation based on root-mean-square

Example: Determination of total Cr in sediments
Units: mg kg^{-1}; *U* for 95 % confidence

[1.5, 10[→ $U = 2\sqrt{0.633^2 + (10 \cdot 0.0450)^2} = 1.6 \text{ mg kg}^{-1}$

[10, 327[→ $U = 2 \cdot 100\sqrt{0.0633^2 + 0.0450^2} = 16 \text{ mg kg}^{-1}$

C. Palma et al., Talanta 192 (2019) 278-287

Evaluation from regulated validation design

Some analytical fields have regulated method validation designs, challenging for the evaluation of the MU.

- Collected data correlation should not affect uncertainty evaluation.

Evaluation from regulated validation design

Example:

Determination of Pd in pharmaceutical products by ICP-MS

Validation according to ICH-Q2(R1) and USP <233> chapter:

Day 1

Replicate analysts of sample with native analyte before and after spiking

Replicate	Concentration (µg/g)
1	4.54
2	4.22
3	4.30
4	4.22
5	4.21
6	4.29
Mean	4.30
RSD	2.9%

Replicate	Level 1 (12.5 µg/g) Concentration (µg/g)	Level 2 (125 µg/g) Concentration (µg/g)	Level 3 (200 µg/g) Concentration (µg/g)
1	17.32	131.82	207.70
2	17.50	135.92	213.98
3	17.84	135.94	213.07
4	17.81	139.64	217.20
5	18.43	134.12	214.34
6	18.92	138.32	215.74

Day 2

Replicate analysts of sample with native analyte after spiking only

Replicate	Level 1 (12.5 µg/g) Concentration (µg/g)	Level 2 (125 µg/g) Concentration (µg/g)	Level 3 (200 µg/g) Concentration (µg/g)
1	16.82	128.22	230.20
2	16.40	142.60	211.53
3	17.19	133.19	213.74
4	16.93	133.36	218.99
5	17.22	137.07	224.10
6	* Outlier: 20.09	134.08	214.48

* - Single Grubbs test outlier for 99 % confidence level

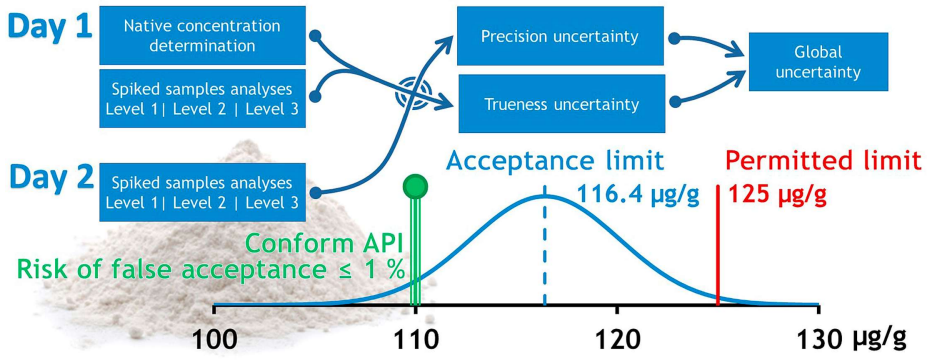
ICH-Q2(R1), Validation of Analytical Procedures, CPMP/ICH/381/95, 1995.

<233> Elemental Impurities Procedures, United States Pharmacopeia, the National Formulary, USP 42-NF37, United States Pharmacopeia Convention, 2019.

Evaluation from regulated validation design

Example:

Determination of Pd in pharmaceutical products by ICP-MS



D. Milde, T. Pluháček, M. Kuba, J. Součková, R. B. Silva, Measurement uncertainty evaluation from correlated validation data: Determination of elemental impurities in pharmaceutical products by ICP-MS, Talanta 220 (2020) 121386

Evaluation from regulated validation design

Example:

Determination of Pd in pharmaceutical products by ICP-MS

experimental data has relevant correlation. For instance, native concentration was determined in the same or different condition as the analysis of spiked samples by analyst 1 and 2, respectively. Therefore, this research shows how the measurement uncertainty evaluation adapts to the specificity of the experimental data instead of being the other way around. The metrological assessment of the measurement problem allows this flexibility although calculations are not necessarily straightforward.

D. Milde, T. Pluháček, M. Kuba, J. Součková, R. B. Silva, Measurement uncertainty evaluation from correlated validation data: Determination of elemental impurities in pharmaceutical products by ICP-MS, Talanta 220 (2020) 121386

Highlights

- Top-down uncertainty evaluations are pragmatic but can be challenging
- The well-known variation of precision with the concentration can be used to divide the analytical range into two intervals ($< \text{ or } \geq 2LOQ$)
- The way bias is managed affect MU
- MU evaluation can adapt to validation design


Thank you for (…)
(…) your attention
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