Measurement Uncertainty -
"Bottom-up" vs "Top-down"

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Introduction

- Where measurement uncertainty comes from
- How uncertainty is assessed in analytical chemistry
  - Propagation of uncertainty
  - Use of method performance data
- Special cases
  - Uncertainties near zero
  - Large uncertainty

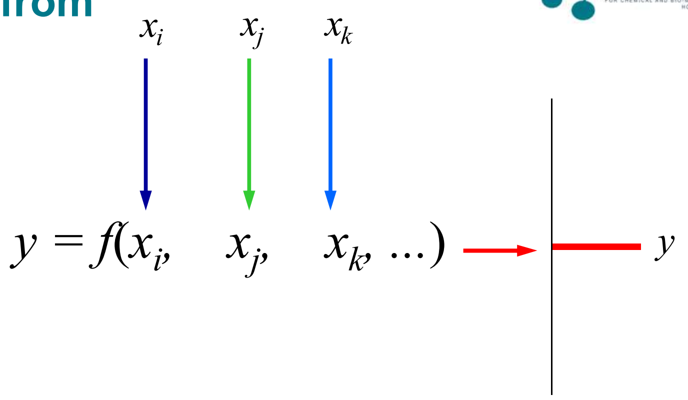
What is Measurement Uncertainty?

"A parameter, associated with the result of a measurement, that characterises the dispersion of the values that could reasonably be attributed to the measurand"

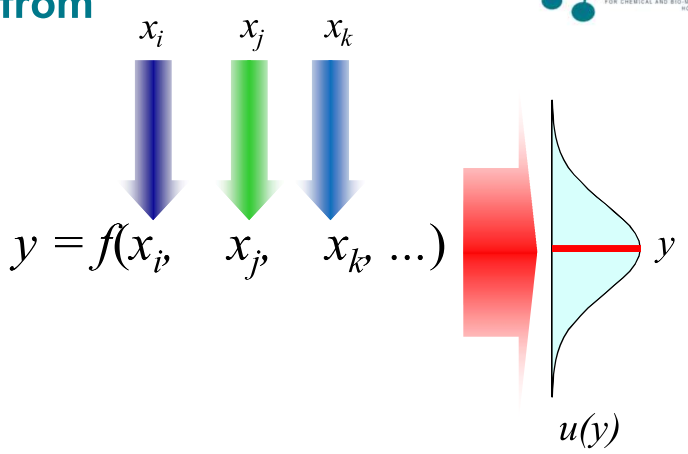
(ISO Guide)

The number after the ±

Where uncertainty comes from



Where uncertainty comes from



Assessing uncertainty: ISO Guide approach

- Specify the measurand
  - including complete equation
- Quantify significant uncertainties in all parameters
  - A: from statistics of repeated experiment
  - B: by any other means (theory, certificates, judgement...)
- Express as standard deviation
- Combine according to stated principles

Sources of Uncertainty

- Sampling
- Sample/matrix effect
- Method
- Extraction/Recovery
- Analyst effects
- Laboratory effects
- Computational effects
- Random effects
- Calibration standards
- Conditions of measurement
- Corrections for known effects

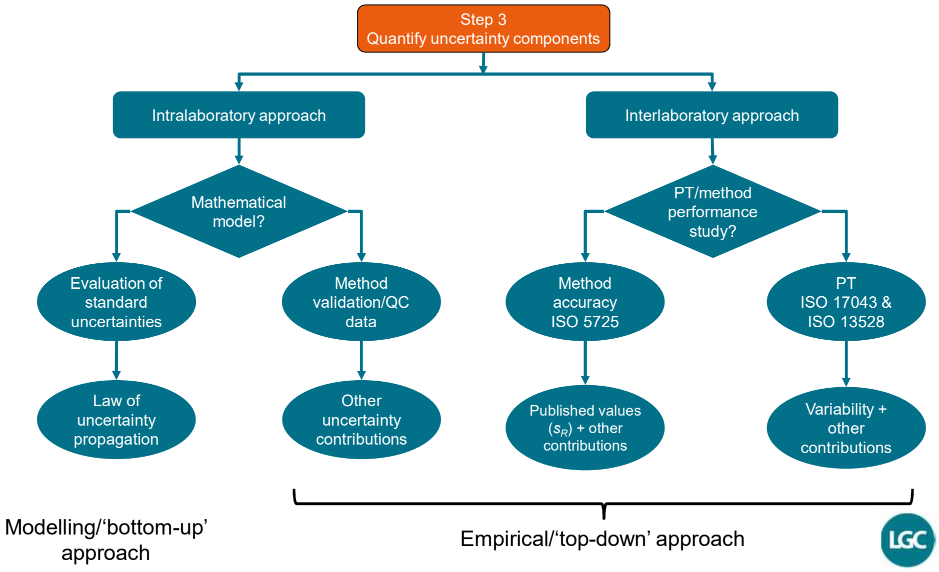
- **Does not include mistakes!**

Estimating uncertainty – general procedure

Step 1 Be clear about what is being measured	Write down equation used to calculate result.
Step 2 Identify the sources of uncertainty	Parameters appearing in the equation will contribute to the uncertainty. What other factors will influence the result?
Step 3 Quantify uncertainty components	Estimate the size of each uncertainty component (the effect it will have on the result). Convert all estimates to the same form (standard uncertainty, *u*).
Step 4 Combine the uncertainties	Combine using rules for combination of variances. $u_c = \sqrt{u_1^2 + u_2^2 + u_3^2 + ...}$
Step 5 Expand combined uncertainty	Multiply the combined uncertainty by a coverage factor to obtain an expanded uncertainty. $U = k.u_c$

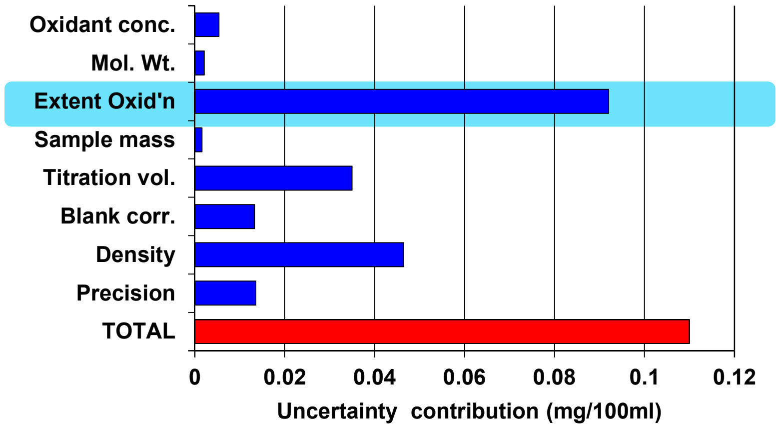
Uncertainty estimation approaches

(adapted from Eurolab Technical Report 1/2007, Figure 1)



A "Top down" example

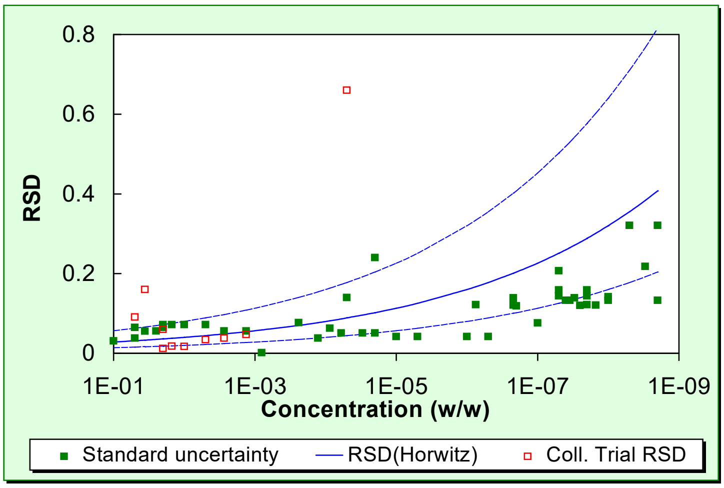
Example: Forensic alcohol standard titration



Implementing ISO in Chemistry Building models

- Every determinand is unique
  - Every element, every molecule, every formulation
- Every ‘matrix’ is unique
  - Different interactions with substrate
- Interactions with environment and substrate rarely understood
- **Models are difficult to build!**

Comparing u with s_R

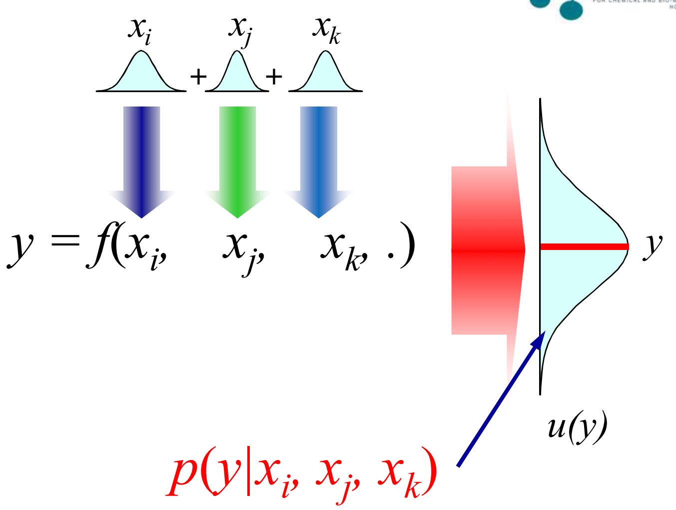


Testing labs underestimate measurement uncertainty using the GUM

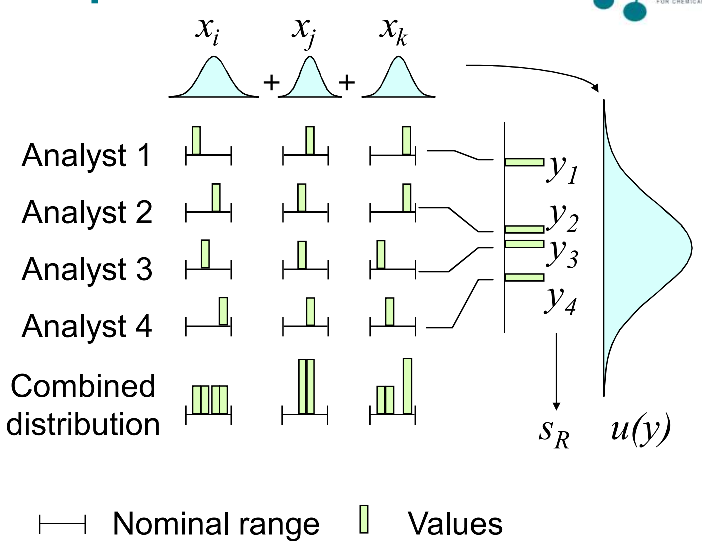
Validation and Interlaboratory studies

- Validation:
  - Experimental studies to establish method performance
  - Aim: Reasonable Assurance of adequacy
- Uncertainty estimation:
  - Experimental and theoretical studies of method performance
  - Aim: Quantification of accuracy

Method performance and MU



Method performance and MU



Real World problems

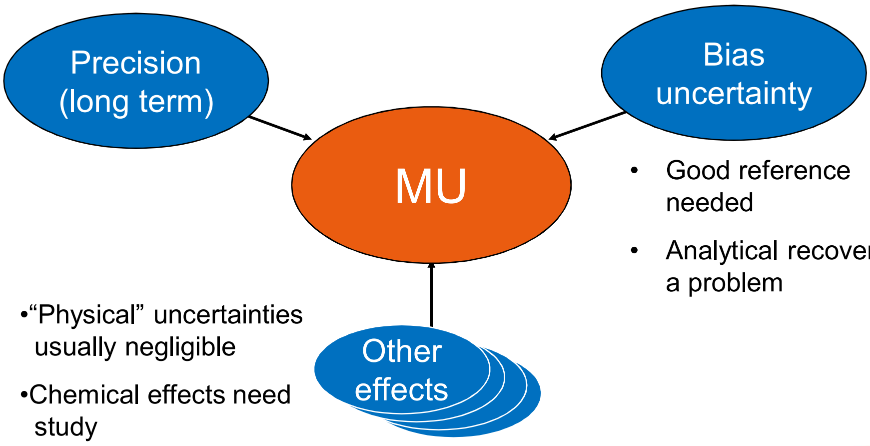
"Well characterised"
quantified effects,
differentiable, continuous,
traceable

Poorly characterised;
Unpredictable effects;
Input parameters unclear

WELL ← **Measurement model applies** → **POORLY**

POORLY ← **Whole method study applies** → **WELL**

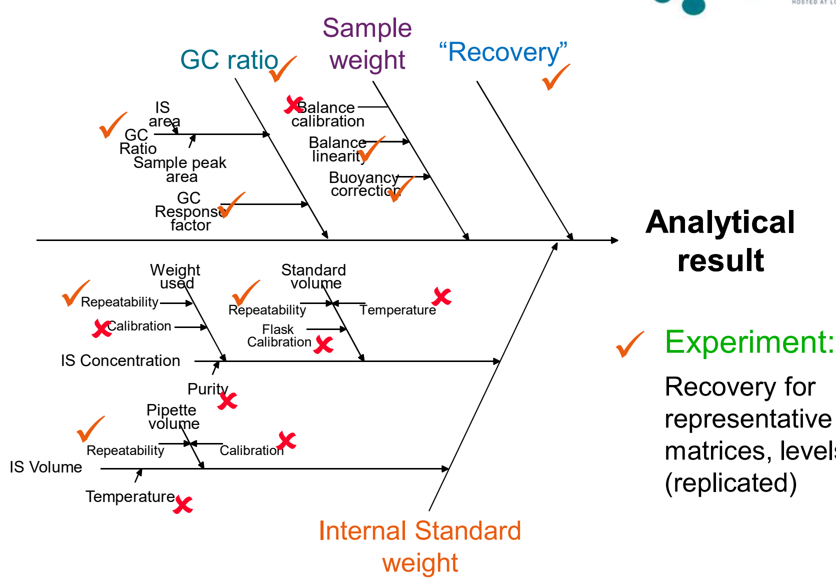
A simpler model



- Good reference needed
- Analytical recovery a problem

- "Physical" uncertainties usually negligible
- Chemical effects need study

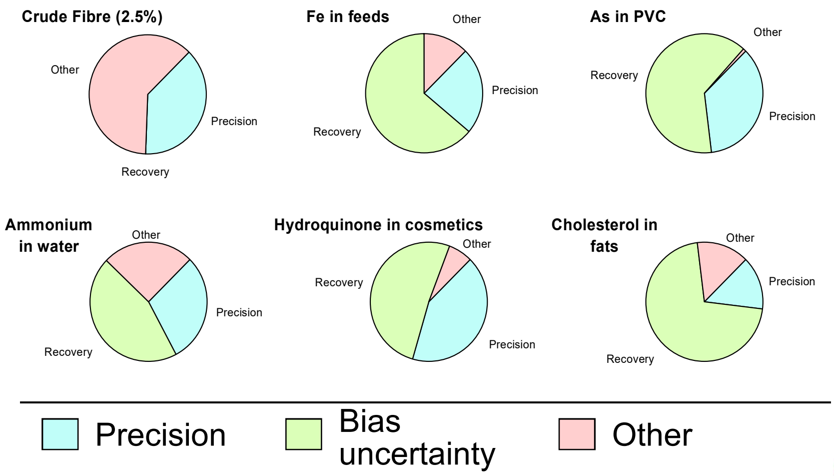
Validation experiment coverage



✓ Experiment:

Recovery for representative matrices, levels (replicated)

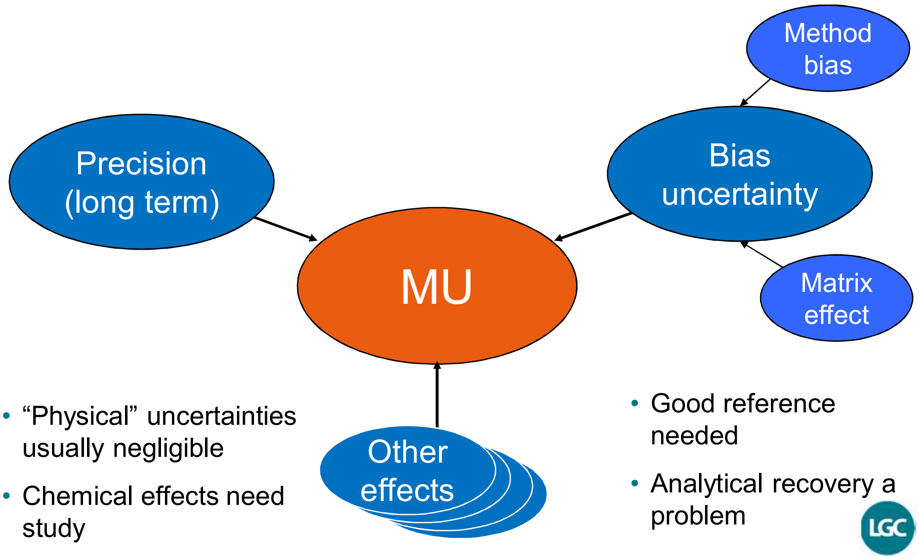
"Precision and Bias" Contributions to uncertainty



Most uncertainty in chemical testing relies on validation data

backed by identification of major uncertainty sources

Using in-house validation data



- "Physical" uncertainties usually negligible
- Chemical effects need study

- Good reference needed
- Analytical recovery a problem

Evaluating precision

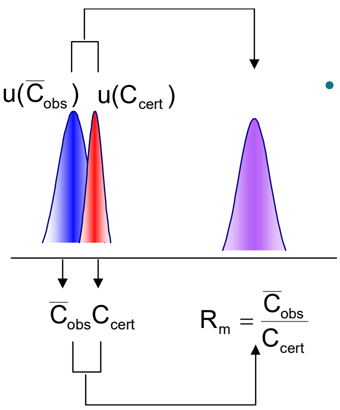
- Aim to cover as many sources of variation as possible
  - extended time period, different analysts, different calibration standards, environmental conditions
- A parameter varied representatively during a precision study requires no further evaluation
- Types of data
  - method validation study (intermediate precision)
  - quality control data – repeated analysis of QC materials
  - data from interlaboratory studies (method validation or PT)
- Need to consider effect of different levels/matrices

Evaluating bias

- A reasonable estimate of the bias can be obtained from
  - validation data (using CRMs or spiked samples)
  - PT data (depending on the nature of the scheme/samples)
- Is the bias significant?
  - statistically significant?
  - significant compared to the method precision?
- Bias and its uncertainty should be considered as part of the uncertainty evaluation process
- Need to consider effect of sample matrix on bias/recovery

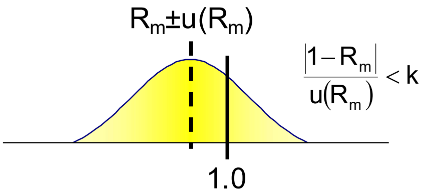
A chemical bias: Uncertainty associated with recovery

$$\frac{u(R_m)}{R_m} = \sqrt{\left(\frac{u(\bar{C}_{obs})}{\bar{C}_{obs}}\right)^2 + \left(\frac{u(C_{cert})}{C_{cert}}\right)^2}$$



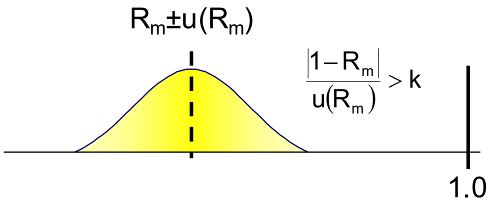
- Estimate of recovery/bias has associated uncertainty
  - uncertainty in reference value $u(C_{cert})$
    - from CRM certificate – convert to standard uncertainty
    - uncertainty in calculated concentration of spiked sample
    - express as a relative value
  - uncertainty in mean of results $u(\bar{C}_{obs})$
    - standard deviation of the mean of results for CRM or spike sample ($s/\sqrt{n}$)
    - express as a relative value

Is there a significant bias?



R_m not significantly different from 1

=> no significant bias



R_m significantly different from 1

=> significant bias

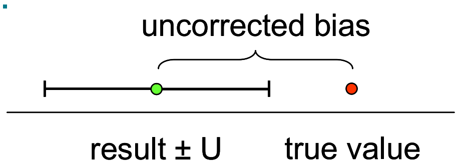
Including bias in uncertainty estimates (1)

- Insignificant bias – recovery not significantly different from 100%
  - assume R_m = 1 with an uncertainty, $u(R_m)$
- Significant bias
  - develop method to remove/reduce bias
  - correct results for known significant bias (ISO Guide)
    - include $u(R_m)$ in uncertainty estimate for corrected results
  - correction uncommon in chemical analysis

Including bias in uncertainty estimates (2)

Uncorrected bias

- Uncertainty is a range which includes the true value….



…so significant bias should not be ignored

Including bias in uncertainty estimates (3)

- If a separate report of bias or recovery is not appropriate
  - increase reported uncertainty by including a bias uncertainty term
  - bias combined with precision using "root sum of squares" rule
- Different approaches proposed for estimating bias term
  - root mean square (RMS) of bias estimates
  - mean bias
  - bias divided by coverage factor, *k*
- Further information in the literature

B. Magnusson, S. L. R. Ellison: Anal Bioanal Chem (2008) 390:201–213
DOI 10.1007/s00216-007-1693-1

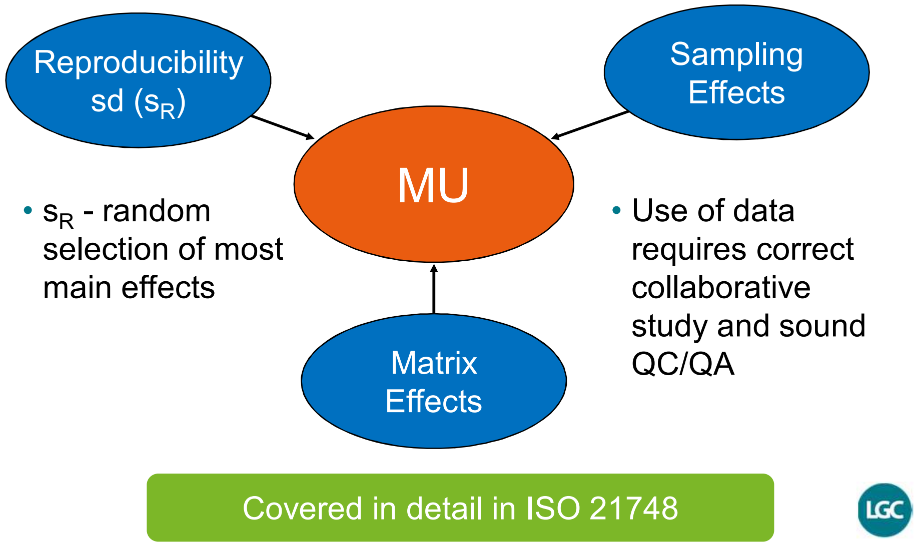
G. E. O'Donnell, D. B. Hibbert DB Analyst (2005) 130:721–729
DOI 10.1039/B414843F

All methods for including uncorrected bias in uncertainty are wrong

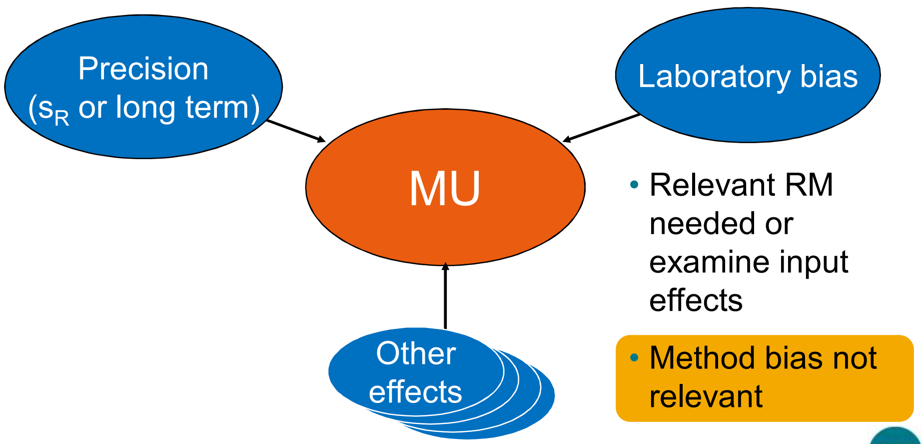
… but some are useful

Some special cases

Collaborative trial data



Empirical methods ("Operationally defined")



Conclusions

- Measurement uncertainty in analytical chemistry can be assessed by
  - Modelling and estimation based on inputs
    Appropriate for metrology labs
  - By observing the actual dispersion in extended experiments
    Best for testing labs