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

\[ y = f(x_i, x_j, x_k, \ldots) \]
Where uncertainty comes from

\[ y = f(x_i, x_j, x_k, \ldots) \]

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.

$$u_c = \sqrt{u_1^2 + u_2^2 + u_3^2 + \ldots}$$

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)

Step 3
Quantify uncertainty components

Intra-laboratory approach

Inter-laboratory approach

Mathematical model?

Evaluation of standard uncertainties

Law of uncertainty propagation

Other uncertainty contributions

Method accuracy
ISO 5725

Published values
\( (u_x)_{\text{other contributions}} \)

Variability + other contributions

PT method performance study?

PT ISO 17043 & ISO 13528

Modeling/'bottom-up' approach

Empirical/'top-down' approach

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

\[
y = f(x_i, x_j, x_k, \ldots)
\]

\[
p(y|x_i, x_j, x_k, \ldots)
\]
Method performance and MU

![Diagram showing method performance and MU]

Real World problems

“Well characterised”
quantified effects,
differentiable, continuous,
traceable

Poorly characterised;
Unpredictable effects;
Input parameters unclear

![Real World problems slide]

Eurachem Cyprus 2020
A simpler model

Precision (long term)  Bias uncertainty

MU

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

Other effects

• Good reference needed
• Analytical recovery a problem

Validation experiment coverage

Analytical result

✓ Experiment:
Recovery for representative matrices, levels (replicated)
Most uncertainty in chemical testing relies on validation data backed by identification of major uncertainty sources.
Using in-house validation data

- Precision (long term)
- Bias uncertainty
- Matrix effect
- Other effects

- "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

\[
\frac{u(R_m)}{R_m} = \sqrt{\left(\frac{u(C_{\text{obs}})}{C_{\text{obs}}}\right)^2 + \left(\frac{u(C_{\text{cert}})}{C_{\text{cert}}}\right)^2}
\]

• Estimate of recovery/bias has associated uncertainty
  – uncertainty in reference value \(u(C_{\text{cert}})\)
    • from CRM certificate – convert to standard uncertainty
    • uncertainty in calculated concentration of spiked sample
    • express as a relative value
  – uncertainty in mean of results \(u(C_{\text{obs}})\)
    • 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?

- $R_m \pm u(R_m)$
- $\frac{|1-R_m|}{u(R_m)} < k$
  - $R_m$ not significantly different from 1
  - $\Rightarrow$ no significant bias

- $R_m \pm u(R_m)$
- $\frac{|1-R_m|}{u(R_m)} > k$
  - $R_m$ significantly different from 1
  - $\Rightarrow$ 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.

\[
\text{result} \pm U \quad \text{true value}
\]

...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
  DOI 10.1007/s00216-007-1693-1

  DOI 10.1039/B414843F
All methods for including uncorrected bias in uncertainty are wrong

... but some are useful

Some special cases
Collaborative trial data

- Reproducibility sd ($s_R$)
  - $s_R$ - random selection of most main effects

- Sampling Effects
  - Use of data requires correct collaborative study and sound QC/QA

Matrix Effects

Empirical methods (“Operationally defined”)

- Precision ($s_R$ or long term)

- Laboratory bias
  - Relevant RM needed or examine input effects
  - Method bias not relevant

Other effects

Covered in detail in ISO 21748
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