Trends in inter-laboratory method validation

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Introduction

- Interlaboratory validation studies
  - Principal international protocols for collaborative study
- Future development of ISO 5725
  - How many samples and replicates are needed?
- The role of Proficiency Testing in method validation
  - Supplementing collaborative study

Current international protocols for collaborative study

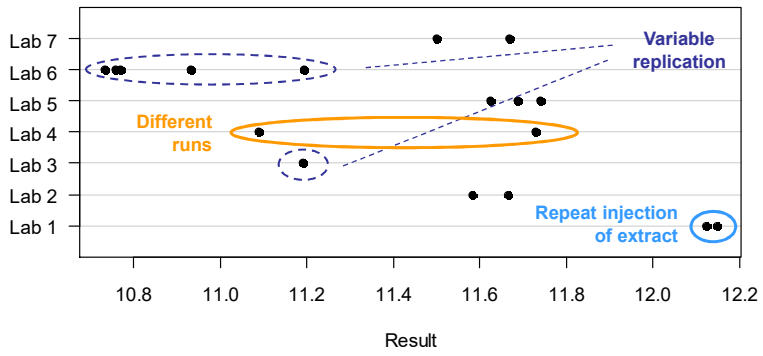
Aims of collaborative study

- To identify factors affecting measurement results
  - Within- or between-laboratory?
- To check that a method can be transferred to other laboratories
- The check that the written protocol is clear to new users
- To estimate the precision characteristics of the method in practice

Typical laboratory study format

- Stable, homogeneous materials distributed to several laboratories
- Laboratories undertake replicate analysis
- Results returned to organiser
- Organiser estimates repeatability and reproducibility
  - ... and, sometimes, trueness

Typical uncontrolled study



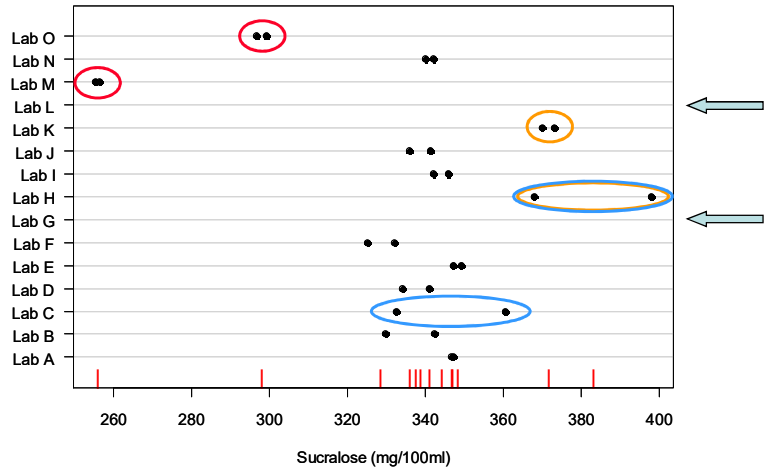
Standards for collaborative study

- ISO 5725: Precision of test methods
  - Part 2: Basic method for the determination of repeatability and reproducibility
- IUPAC: Protocol For The Design, Conduct And Interpretation Of Method-Performance Studies

IUPAC recommendations

- Minimum of 8 laboratories
  - 5 in exceptional circumstances
- Minimum of 5 test materials
  - 3 under some conditions
- Replication specified in preference order:
  1. Split level (slightly different samples)
  2. Combination blind replicates and split level
  3. Blind replicates (Separate samples, no visual cues)
  4. Known replicates
  5. Independent analyses
     - 1 replicate, repeatability determined separately

Typical data from standardized study design



Data treatment recommendations

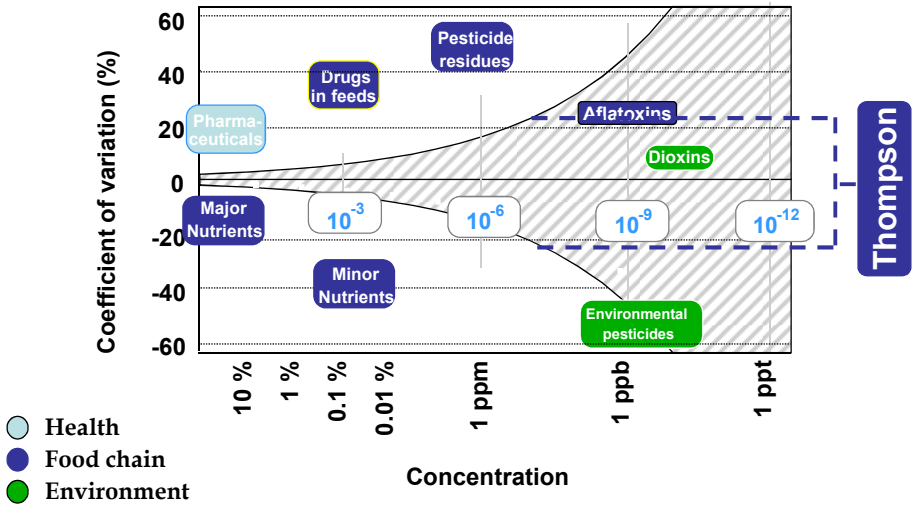
- Outlier testing
  - Cochran (for excess variance)
  - Grubbs tests (for extreme mean values and pairs of means)
- Outlier action
  - IUPAC: Remove at 97.5% confidence
  - ISO 5725: Inspect at 95%; Remove at 99%
- Repeated outlier tests
  - Permitted to maximum of 22.2% data set loss (IUPAC)

Results

- Processing using 1-way analysis of variance gives:

mean	347.10	
r	26.68	2.8 s_r
sr	9.53	
RSDr	2.74	s_r/mean (%)
H0r	0.63	
R	48.64	2.8 s_R
SR	17.37	
RSDR	5.00	s_R/mean (%)
H0R	0.75	

Horwitz predicted %RSD



What does collaborative study tell us?

- The precision of results after removing outliers
  - Precision when no-one makes a mistake?
- ***NOT*** the dispersion of all results

- How precision changes with concentration
  - APPROXIMATELY across many methods

- How precision compares with past practice or with a requirement

Development of ISO 5725

Proposed revisions

Current ISO 5725 structure

- Part 1: Concepts and definitions
- Part 2: Basic method – single (laboratory) grouping factor
  - Very widely used
- Part 3: Multi-level layout
- Part 4: Trueness
- Part 5: Alternative methods
  - Simple, early robust method and staggered-nested layout
- Part 6: Use in practice of accuracy values

The changed environment

- Amended terminology – ISO 3534 and others
- Computers on every desk
- Basic ANOVA tools and free statistical software widely available
- REML now recommended* for most variance estimation problems
- Wider range of robust estimation methods
  - Including unbalanced and multi-level designs
- Accreditation increasingly important in laboratories
  - Increased emphasis on in-house validation, measurement uncertainty, within-lab precision etc

**Searle, Casella, Murdoch, Variance components, Wiley, 2006*

Unchanged

- Location outliers endemic in interlaboratory studies
- Within-lab precision rarely constant
  - and sometimes anomalously large
- Collaborative study important for test method development in most sectors
- Statistical expertise limited in many sectors

Some ‘missing’ elements in 5725-2

- Minimum study size
- Recursive outlier assessment
- ‘Stopping’ criteria for repeated outlier examination
- Computer-based calculation procedure
  - No use of ‘standard’ ANOVA table
- REML
- A linear variance model for precision
- Confidence intervals for variance estimates
- Calculation methods for critical values (eg Mandel indicators) for computer implementation

Proposed ISO 5725 evolution

- Part 1: Updated for consistency with international terminology
- Part 2: Preserve procedure
  - permission for some limited alternatives
  - Additional information on study size etc.
- Part 3: Retain within-lab; combine different **designs**
  - Split-level; staggered-nested
- Part 4: Trueness - retain
- Part 5: To cover alternative **data handling methods**
  - Widen robust methodology
- Part 6: Use in practice of accuracy values
  - No current plans for change

The role of PT in method validation

Interlaboratory study formats

Validation

- Stable, homogeneous materials distributed to several laboratories
- Laboratories undertake replicate analysis **using one method**
- **Replicate** results returned to organiser
- Organiser estimates repeatability and reproducibility

Proficiency

- Stable, homogeneous materials distributed to several laboratories
- Laboratories undertake replicate analysis **using any method**
- **Single or replicate** results returned to organiser
- Organiser assigns value and 'scores' labs

Could PT data replace or supplement validation studies?

Advantages and Disadvantages of PT for method validation

Advantages

- More frequent
- Often many more laboratories
- Already required for most laboratories

Disadvantages

- Free choice of methods
- Typically requires single values (no replicates)
- Few materials per round
- Methodology detail not always collected

RSC Analytical Methods Committee: Some key recommendations*

- At least part of the population assessed by PT must be using the analytical method of interest
- Use of proficiency testing data for method performance assessment should not be allowed to modify the PT design
- Number of materials and participants ... should be at least consistent with minimum requirements for collaborative study
- Replication within a scheme round is not required
  - but it is desirable
- Methodology detail should be collected

*Accred Qual Assur (2010) 15:73–79
DOI 10.1007/s00769-009-0560-5

AOAC use of PT*

- 2011 – Alternative pathway to 'First Action'
  - (Preliminary adoption of a standard method)
- Methods adopted 'First Action' by Expert Review Panels
- Method in First Action Status and Transitioning to Final Action Status:
  - Further data indicative of adequate method reproducibility (between laboratory) performance to be collected.
  - Data may be collected via a collaborative study or by proficiency or other testing data of similar magnitude.

*http://www.aoac.org/imis15_prod/AOAC_Docs/StandardsDevelopment/FAOMA_Requirements.pdf
Accessed 25 Apr 2016

Summary

Conclusions

- Collaborative study is still the approach of choice for international standard methods
- ISO 5725 is under revision
  - Part 2 to be preserved; other parts widen options for design and data treatment
- Proficiency test data can be used (with care) to gather data on inter-laboratory performance
  - Some international organisations trialling PT data for validation/approval support