Setting standards in analytical science

World class
research and technology

Research & Technology

Measurements for Regulation: The Roles of Analytical Quality and Measurement Uncertainty

Introduction

Setting standards in analytical science

- Measurement in regulation
- Limit setting in regulation
- Measurement uncertainty - what and how
- Uncertainty: impact on regulation
- Responsibilities

Why regulate?

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- To reduce risks to health and environment
- To control trade and prevent fraud

Both require only "Reasonable assurance"

"Reasonable assurance"

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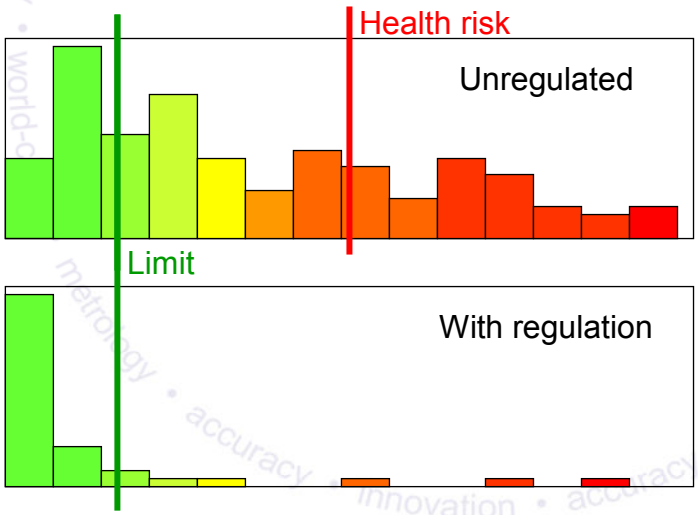

Why measure?

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- Ensuring compliance with regulation is the most frequently reported reason for undertaking analysis
  - (May be in conjunction with others)
- Analytical results support compliance with regulatory limits

Why worry?

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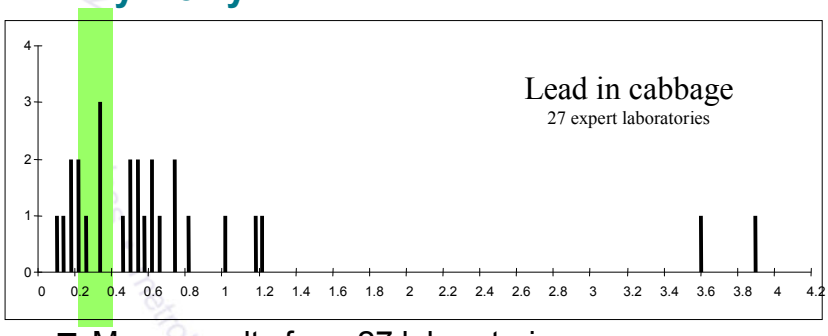
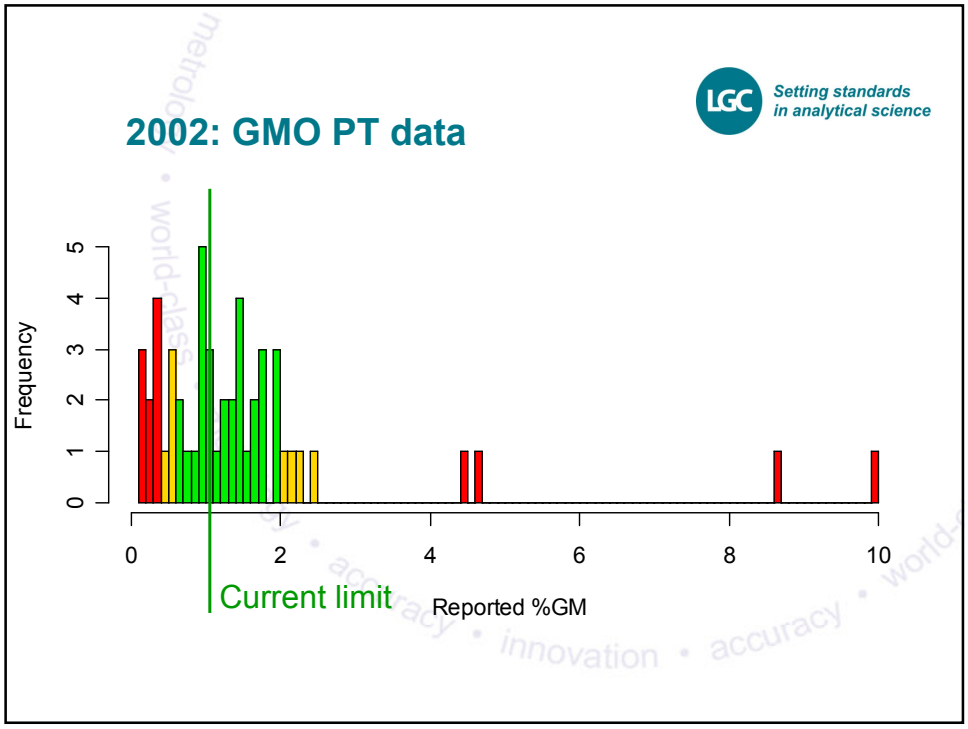
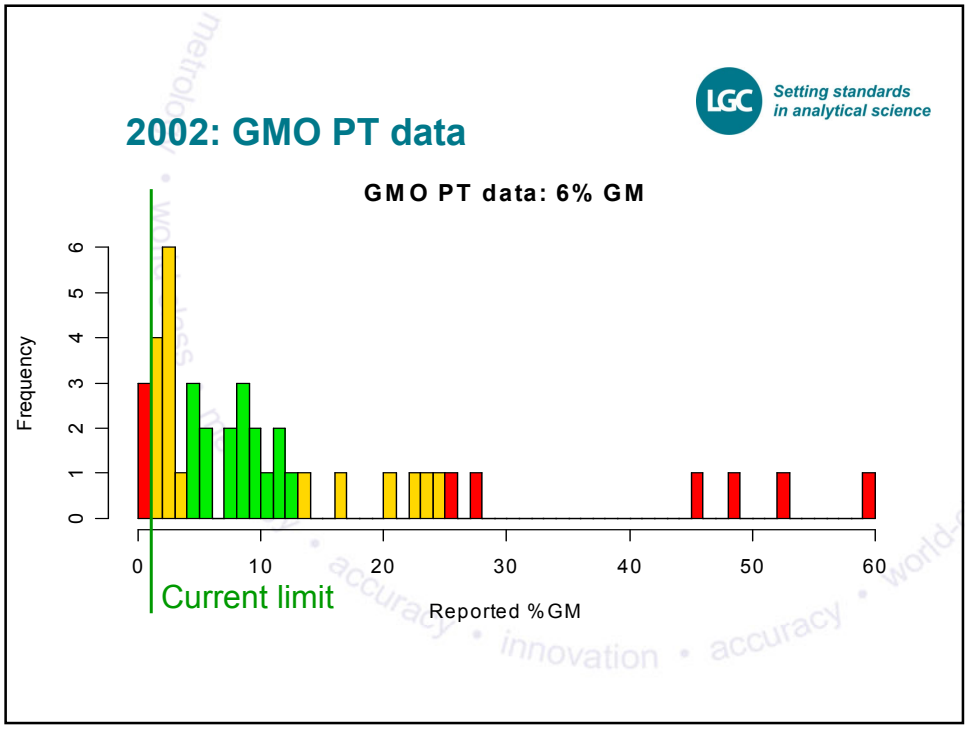


- Mean results from 27 laboratories
- Acceptable range 0.23 - 0.41 $mg.kg^{-1}$
- 4 laboratories within acceptable range


Setting standards
in analytical science
2002: GMO PT data
Frequency
0
1
2
3
4
5
0
2
4
6
8
10
Current limit
Reported %GM


Setting standards
in analytical science
2002: GMO PT data
GMO PT data: 6% GM
Frequency
0
1
2
3
4
5
6
0
10
20
30
40
50
60
Current limit
Reported %GM

Improving quality - VAM* Principles

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- Agreed requirements
- Method Standardisation and validation
- Traceability through measurement systems and reference materials
- Quality systems
- Proficiency testing
- Training and competence

"Metrology"

*http://www.nmschembio.org.uk/

Standardisation

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- Standard method developed
- Performance tested in-house
- Checked by interlaboratory comparison
- Accepted for specific scope and field of application
  - Scope: analyte, matrix/substrate, level
  - Field: purpose of analysis

Standardisation: Pros & Cons

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Pro:

- Specific to application
- May allow definitive/empirical method
- Relatively simple to implement once developed

Con:

- Takes time - >1 year for regulatory methods
- Lowest common denominator approach
- Limits technological innovation
- Hard to agree across borders
- May need continuous verification

Method Validation

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"**A decision on fitness for purpose supported by experimental evidence**"

- Implementation
  - Applied to methods with defined scope
  - Determines a range of performance characteristics
  - Judges fitness by comparison

Equivalence through traceability

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- Traceability:
  Property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty.
- Key “References”
  - Calibration standards
  - Traceable reference materials for independent checks

Common references

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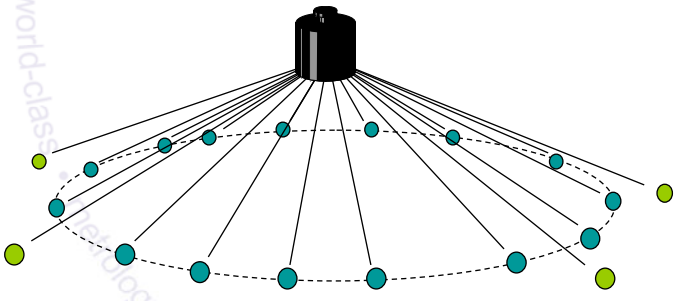

Laboratories

Hierarchical Measurement System

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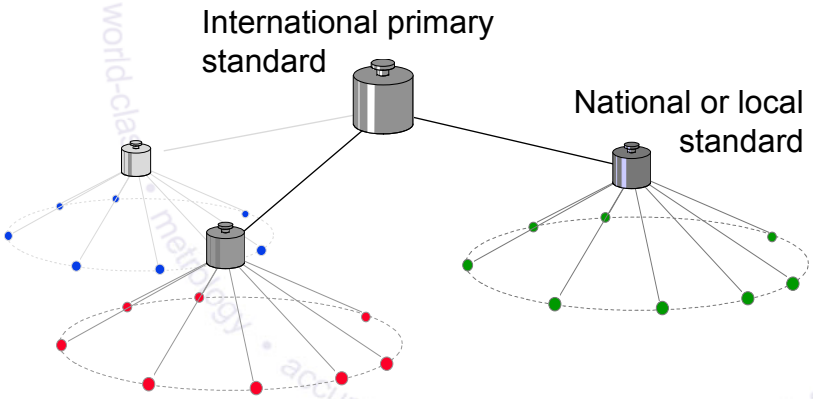

Practical implementation - International agreement

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- BIPM CCQM
  - Consultative Committee for Quantity of materials
- Establishes methods and agreement among National Measurement Institutes
- Agreement allows acceptability across borders
- Reference laboratories can provide reference measurements and materials

Key Comparison development

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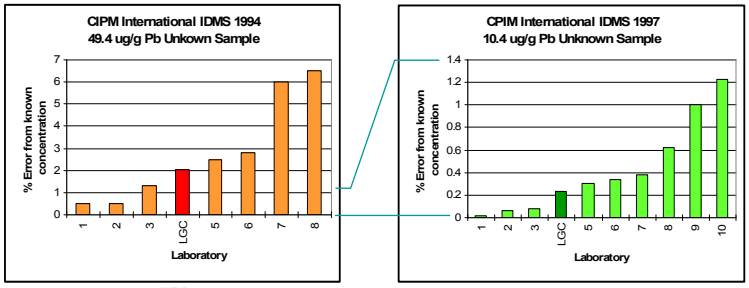

Round 1: 1994

Round 2: 1998

Practical implementation - Reference materials

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- CRM definition
- Well established value
- Stable, homogeneous material
- Used for calibration or testing performance

Quality systems

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- ISO 9000: Consistency and contract
- GLP/GMP: Documentation and (via cGMP) technical requirements
- ISO 17025 (“Accreditation”): Technical competence
- Monitored by Accreditation Bodies or GxP approval bodies
- Mandatory for most important measurements

Training and Competence

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- All quality systems require appropriate training
- Technology transfer happens best through
  - PEOPLE MOVING
  - PEOPLE COMMUNICATING
- Continued dialogue works better than one-way specification
- Proficiency testing promotes technical dialogue

Intercomparison by Proficiency testing (EQA)

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- Pros:
  - Not necessarily method-specific
  - Tests complete measurement/reporting process
- Cons:
  - Requires sufficiently stable material
  - Infrequent - monthly

Measurement uncertainty estimation

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- One of the most important tools for practising metrologists
- "Predicts" the dispersion of results
- Provides a guide to interpretation
- … and is now required by all accreditation bodies
- … even in analytical chemistry and biological measurement

What is Measurement Uncertainty?

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"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 ±

Measurement uncertainty ...

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- DOES NOT
  ...just include observed precision
- DOES
  ... include ALL POSSIBLE effects
  ... including uncertainties in reference values, environment, method controls....
  ... *try* to say something about where the true value might lie

Problems

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- "Correct" evaluation
- Impact on compliance assessments
- Communication
- Management
  - of uncertainty
  - of decisions with uncertainty

Uncertainty evaluation methods

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- Repeatability assessment
  - Always insufficient...
- ISO Guide approach
  - Accreditation
- Validation-based approaches
- Interlaboratory study
  - Traditional in regulatory analysis

ISO Guide approach

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- 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
- Multiply by “coverage factor”

Combining uncertainties (ISO)

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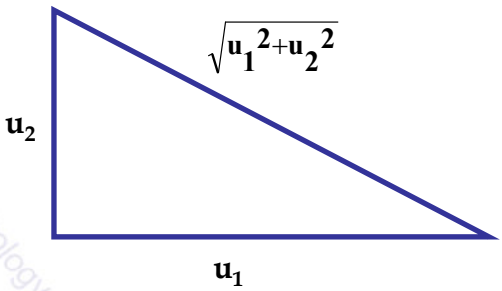

- *Standard deviations*
- *Established error propagation theory*

Example: Forensic alcohol reference standard titration

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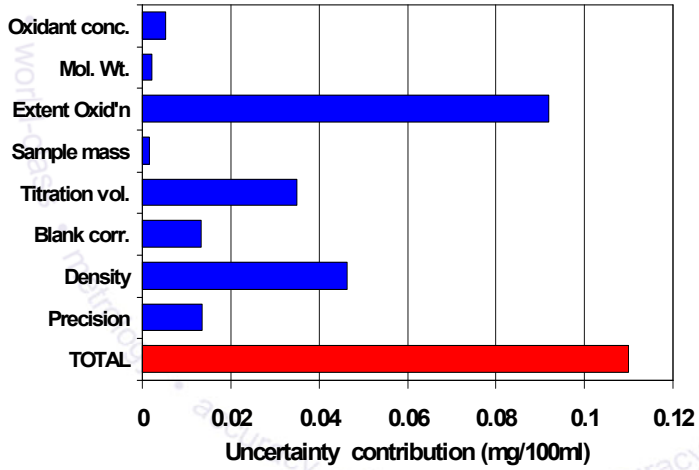

Validation and Interlaboratory studies

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- Validation:
  - Experimental studies of method performance
  - Aims: Check model assumptions: Reasonable Assurance of adequacy
- Uncertainty estimation:
  - Experimental and theoretical studies of method performance
  - Aim: Quantification of accuracy

MU based on validation

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- The best available estimate of precision
  - *An effect varied representatively during a precision experiment requires no further study*
- The best available estimate of bias *and its uncertainty*
- Other significant effects evaluated
  - By experiment, or from standing data

Collaborative Study basis

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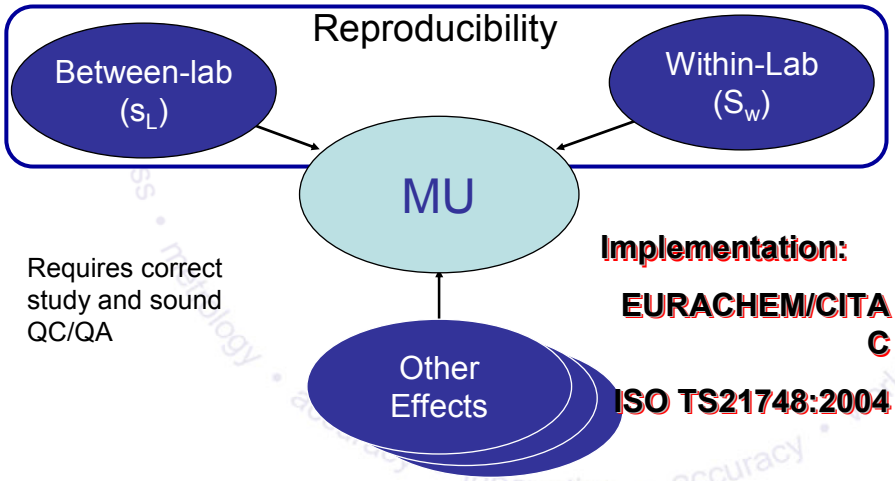

Requires correct study and sound QC/QA

Implementation:

EURACHEM/CITAC

ISO TS21748:2004

"Best" Method depends on the problem

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"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**

Comparing *u* with s_R

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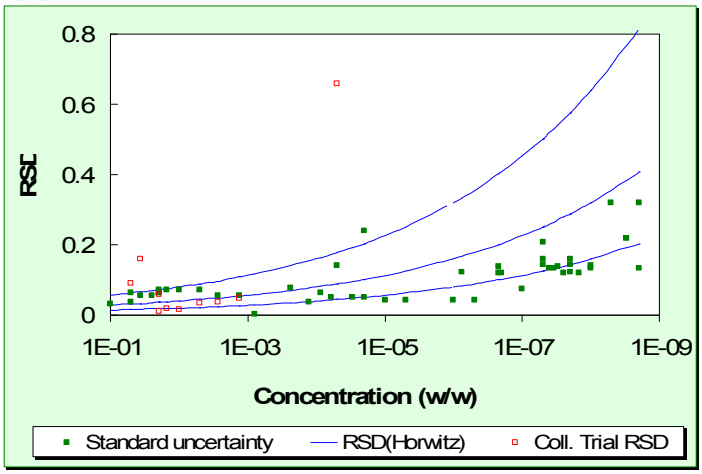

What does Uncertainty mean?

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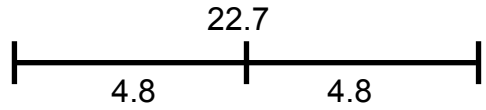
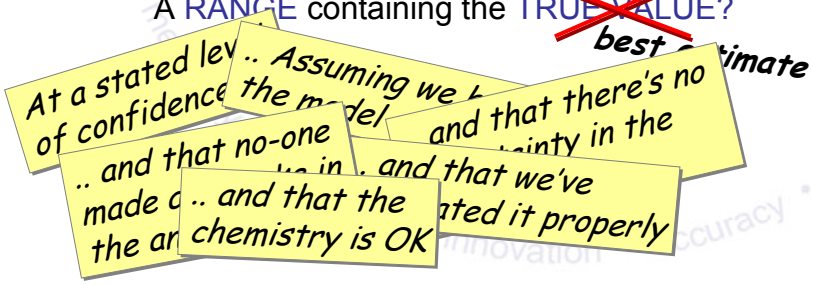
22.7 ± 4.8 g



"The amount is between 17.9 and 27.5"

A RANGE containing the ~~TRUE VALUE~~ best estimate?



What does Uncertainty mean?

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- That the result is uncertain so we can ignore it
- That the
- That mo
- That we results
- That we
- ….

Measurement uncertainty is a guide to safe interpretation

Impact on regulation and compliance

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- Changes in interpretation
- Ambiguity
- Credibility and communication

Interpretation

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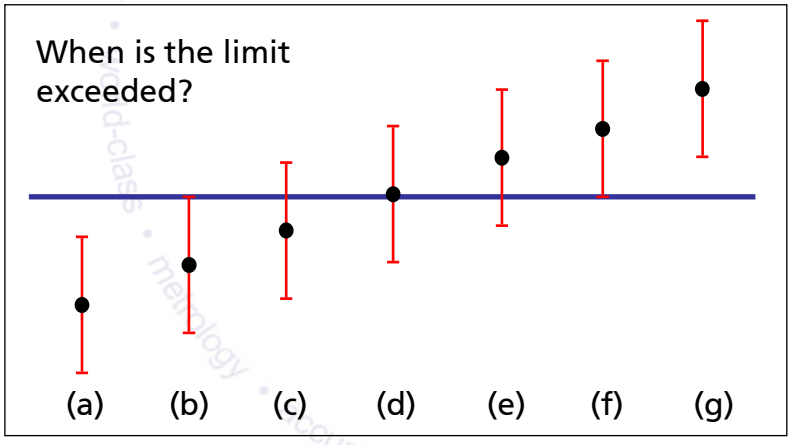

Positive compliance/ non-compliance

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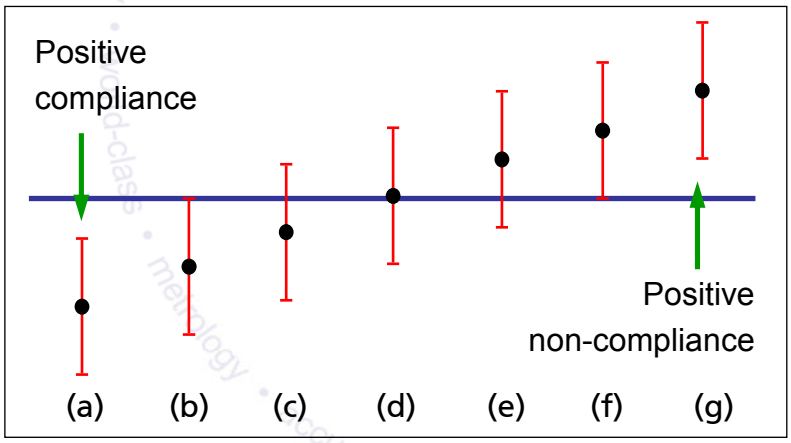

Interpretation: example

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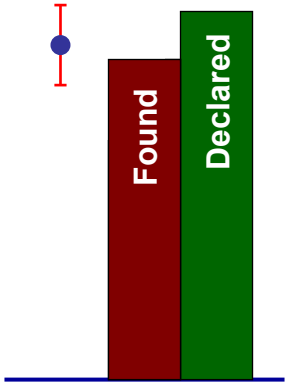
- Declared Meat Content: 67%
  - Public Analyst result: 64%
  - LGC Referee result: 65±3%
  - Trading Standards officer correspondence:

> This vague answer has prevented a successful prosecution… **has anyone else experienced these ambiguous results from LGC?**



Managing uncertainty in regulation

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- Know the uncertainty
- Establish rules for interpretation
  - Whether to use uncertainty
  - How to evaluate
  - Positive compliance versus positive non-compliance

"Reasonable assurance" and uncertainty

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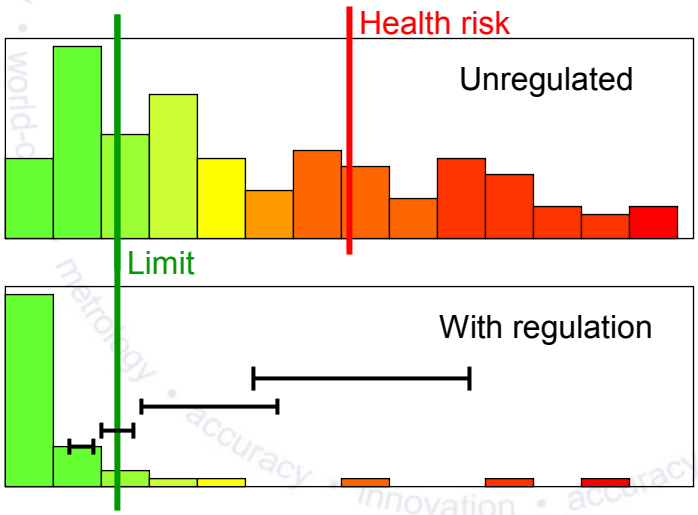

Managing uncertainty: Rules for interpretation

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- Ignore uncertainty
- Incorporate uncertainty in limit

Regulators and tech experts must establish acceptable uncertainty and demonstrate it

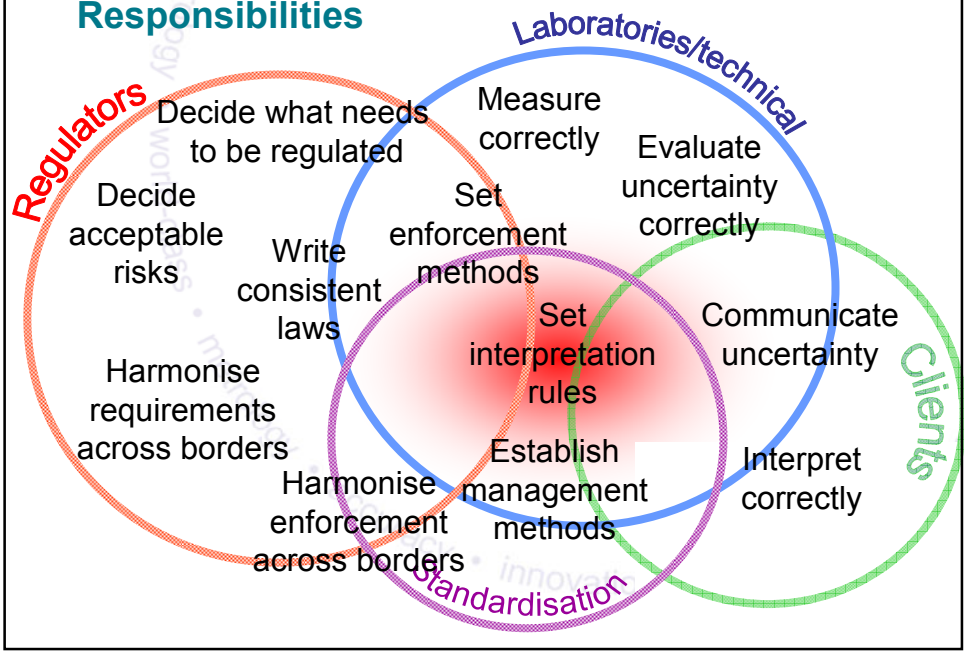
- Require uncertainty reporting

Labs estimate uncertainty; regulators/experts decide how and set interpretation rules

- Require expert interpretation

Labs must become experts; usually includes knowledge of MU

Responsibilities



Best practice - do them all!

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- Validated & tested methods
  - Right measurement, properly tested
- Reference materials
- Proficiency testing
- Measurement uncertainty
- Accreditation
  - Checks Technical competence
  - Quality system covers QC, QA, Training, etc..
- Regulators: use the results wisely

Performance improvement: Lab's view

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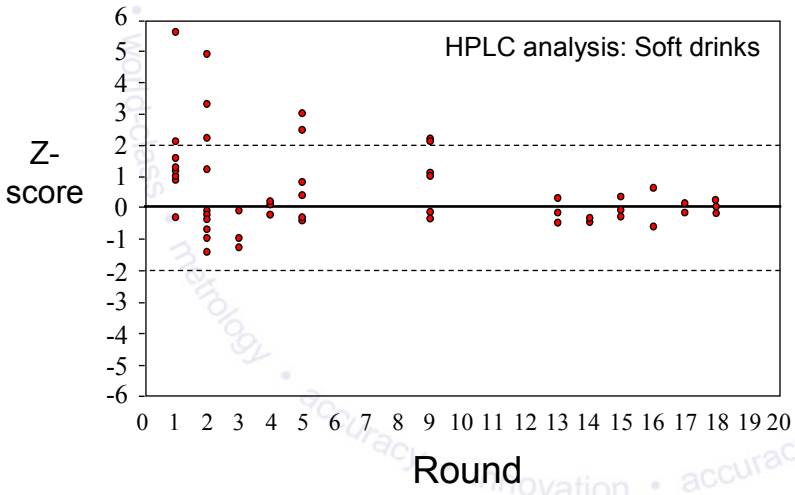

Summary

Setting standards in analytical science

- Comparability is essential to trade, legislation and good science
- Comparability is checked by intercomparison and assured by validation and traceability
- Measurement uncertainty guides interpretation
- …. but introduction creates ‘new’ questions for analysts and enforcers
  - Evaluation methods
  - Reporting and interpretation