IAEA Workshop on Nuclear Data for Activation Analysis
Abdus Salam International Centre for theoretical Physics
7-18 March 2005, Miramare – Trieste, Italy

Error propagation and quality assurance

Lecture notes

Borut Smodiš

Jozef Stefan Institute
Ljubljana, Slovenia

Quality Assurance: "All the planned and systematic actions implemented within the quality system, and demonstrated as needed, to provide adequate confidence that an entity will fulfil requirements for quality."

Quality control: "Individual measures which relate to the monitoring and control of particular analytical operations."

Quality system: "The organisational structure, procedures, processes and resources needed to implement quality management."

Quality: "Satisfying customers' needs", "fitness for purpose", "getting it right first time".
Defined quality criteria enable judgments to be made against defined minimum standards or on a ranking basis. An element of scientific excellence is involved but there must also be a trade off involving cost and time. Sources of quality evidence may include:

- Scientific reputation/ability to win contracts
- Work practices
- Staff qualification, experience, attitudes
- Quality systems, audit, review and accreditation

Analytical quality assurance

At the technical level there are many quality requirements ranging from the validation of methods to the calibration of equipment and the establishment of the traceability of measurements.

Principles for making valid analytical measurements:

1. Analytical measurements should be made to satisfy an agreed requirement
2. Analytical measurements should be made using methods and equipment which have been tested to ensure they are fit for purpose
3. Staff making analytical measurements should be both qualified and competent to undertake the task
4. There should be regular independent assessment of the technical performance of a laboratory
5. Analytical measurements made in one location should be consistent with those made elsewhere
6. Organisations making analytical measurements should have well defined quality control and quality assurance procedures

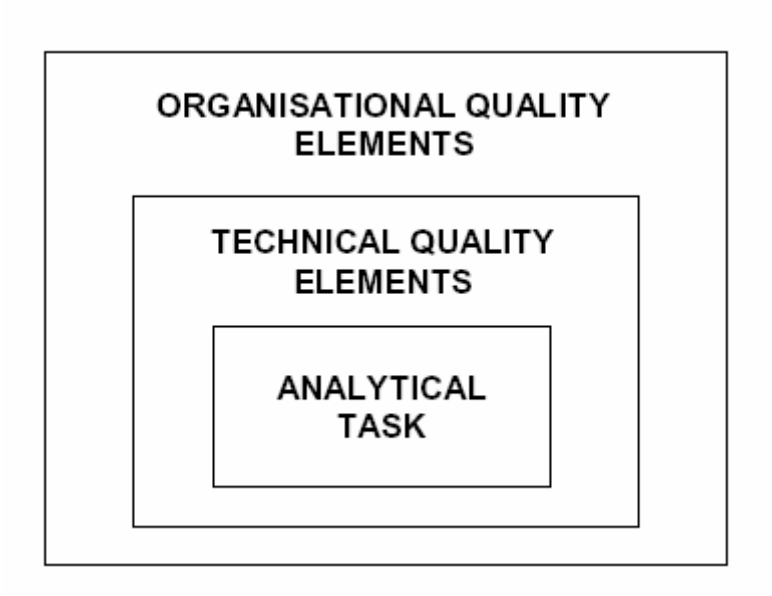


Fig.1

Figure 1 shows a hierarchical approach to quality assurance within an organisation.

1. Organisational quality elements apply to all levels of activity within an organisation. Examples include a quality management structure with a defined role within the organisation; a quality system; documented procedures for key activities; recruitment and training policy for all staff, etc. The elements comprise the following issues:
    a. Administrative and technical planning of the work
        i. Suitable staff
        ii. Coordination in using facilities
    b. Quality management, corporate and local
        i. Formal or informal quality management system, organisational structure
        ii. Balance between control and creativity
    c. Record keeping and document control

Level	Documentation	Subject / examples
1. (Highest)	Corporate quality policy	Quality manual
2.	• Formalised internal procedures operable across the laboratory	Standard Operating Procedures (SOPs)
	• Other (external) normative documents	Relevant laws, regulations, standards (ISO/CEN *etc.*), official methods (e.g. AOACI), Codes of Practice (COPs).
3.	Technical work instructions (specific applications)	In-house methods
4. (Lowest)	Records	Instrument logbooks, calibration records laboratory notebooks and other raw data, correspondence, reports

    d. Staff qualifications, training and supervision

    e. Equipment
    f. Monitoring quality
    g. Subcontracting
2. Technical quality elements comprise specific QA elements, which apply to the technical activities of the organisation, such as policy and procedures for instrument calibration and performance checks, use of calibrants and reference materials, and use of statistical procedures. The elements comprise the following issues:
    a. Unit operations (modular approach)
    b. Technical capability of the laboratory
    c. Methodology (SOPs)
    d. Reagents, reference materials, and calibrants
    e. Calibration and traceability
    f. Instruments performance
    g. Use of statistics
        i. Experimental design
        ii. Characterisation of method performance and determination of uncertainty
        iii. Development of quality control
        iv. Interpretation of results
    h. Technical requirements related to particular unit processes
        i. Sampling
        ii. Isolation of the analyte(s) using separation and enrichment
        iii. Measurements
        iv. Validation
        v. Measurement uncertainty
3. Analytical task quality elements represents the activities carried out for particular projects or individual analytical tasks. It includes the planning, control, and reporting practices recommended at the start of, during, and at completion of work. The elements comprise the following issues:
    a. Preparation and planning before starting work
        i. Definition of task and project design
        ii. Project design and research plan
        iii. Resource management of task
    b. While the work is in progress
        i. Progress review/monitoring analysis
        ii. Data verification
        iii. Changing direction
    c. When the work is complete
        i. Achievement review
        ii. Reporting, technology transfer and publication
        iii. Archiving
4. External verification
    a. Formal assessment against published quality assurance standards
        i. ISO Guide 17025
        ii. ISO 9001
        iii. GLP
    b. Benchmarking

Method validation

Method validation. “A process (set of tests) that test: (1) any assumptions on which the analytical method is based and (2) document the performance characteristics of a method, thereby demonstrating whether the method is fit for a particular analytical purpose.

Why is method validation necessary?

- Importance of analytical measurement
- Professional duty of the analytical chemist

When should methods be validated?

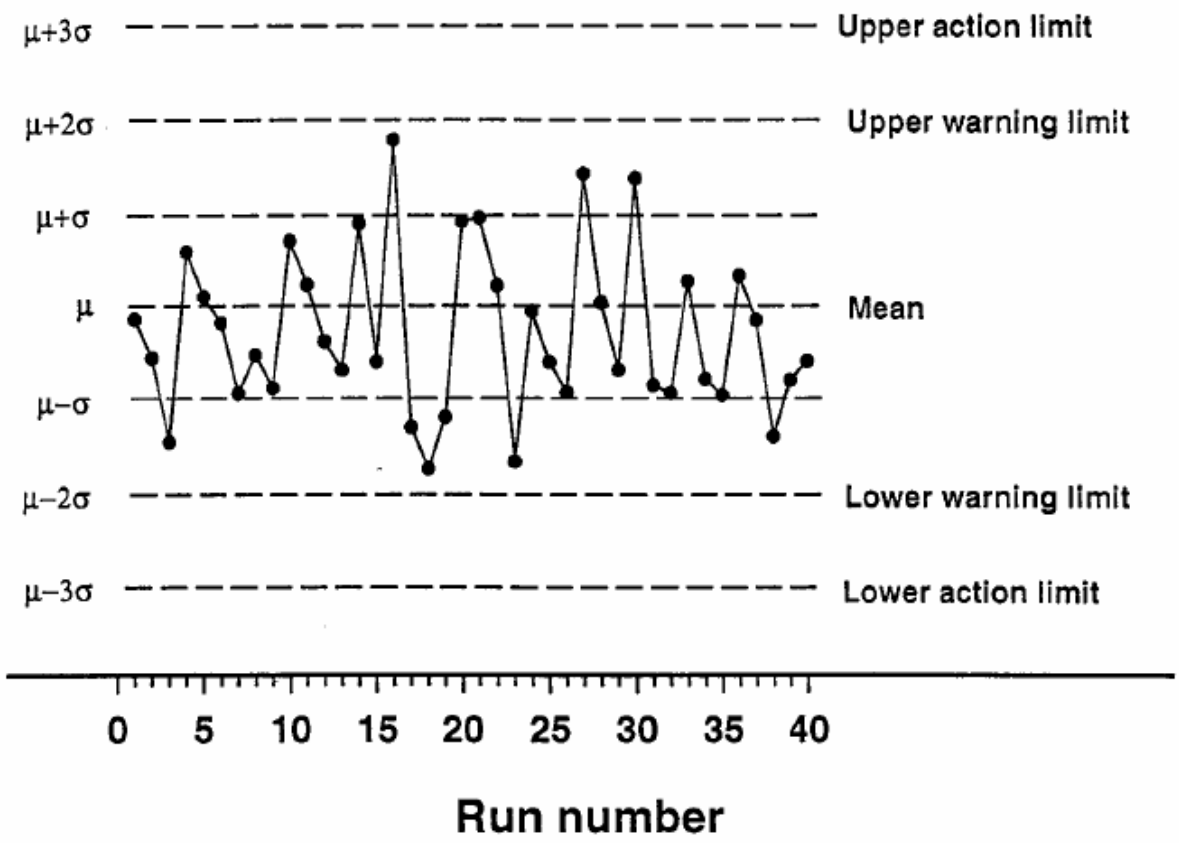
How should method be validated?

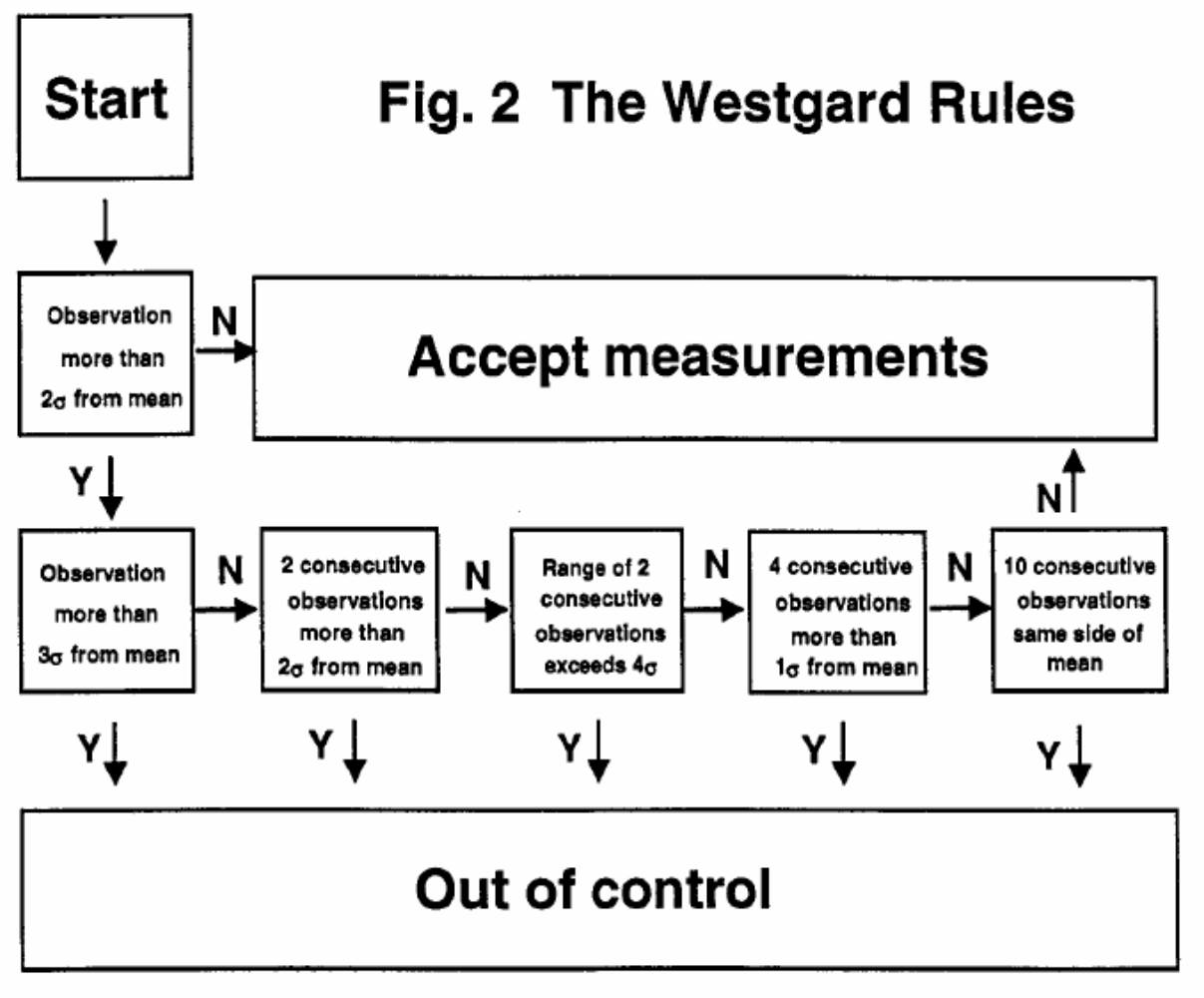
- Who carries out method validation
- Deciding what degree of validation is required
- The analytical requirement
- Method development
- Performance parameters of a method
    - Confirmation of identity and selectivity/specificity
    - Limit of detection
    - Limit of quantitation
    - Working and linear ranges
    - Trueness
    - Interpreting bias measurements
    - Reproducibility
    - Measurement uncertainty
    - Sensitivity
    - Ruggedness (robustness)
    - Recovery
- Tools of validation
    - Blanks (reagent, sample)
    - Samples / test materials
    - Fortified materials / solutions
    - Spiked materials
    - Incurred materials
    - Independently characterised materials
    - (Measurement) standards
    - Reference materials
    - Certified reference materials
    - Statistics
    - Replication
- Using validated methods
- Using validation data to design QC
    - Internal quality control. “Set of procedures undertaken by laboratory staff for the continuous monitoring of operations and the results of measurements in

order to decide whether results are reliable enough to be released." Statistical control, fitness for purpose.

- Blanks
- Chemical calibrants
- Spiked samples
- Replicate analyses
- QC samples

Fig. 1. Results from a system in statistical control



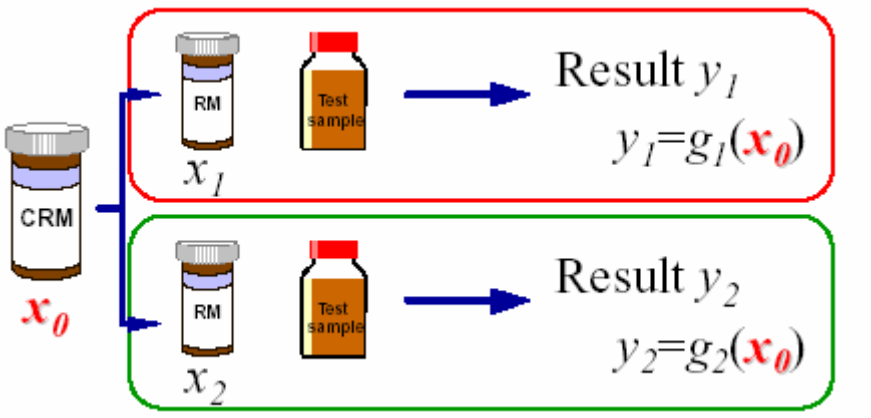


- External QC
  - Proficiency testing
  - ILC
- Documentation of validated methods
- Implications of validation data for calculating results and reporting

Traceability in chemical measurement

Traceability is property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or international standards through an unbroken chain of comparisons (= traceability chain) all having stated uncertainties.

1. Principles of traceability
    a. Methods, Measurands and Results
        i. Measurands is a "quantity subjected to measurement", such as mass, volume or concentration.
        ii. Methods are procedures intended to provide estimates of the values of measurands.
        iii. Results are values ascribed to measurands following measurement using an appropriate method.
    b. Measurement scales, standards and units
    c. Calibration
    d. Effects on measurement results
    e. Controlling fixed conditions
    f. Controlling variables with calibration standards



    g. Common references allow arbitrary definition
    h. Role of method development
    i. Role of method validation
    j. Traceability and measurement uncertainty
2. Establishing traceability
    a. Specifying the measurands and required uncertainty
        i. Identity of the analyte
        ii. Implied measurement conditions
        iii. Recovery correction
        iv. Specification in terms of a method
    b. Choosing a suitable method
    c. Validation
    d. Importance of different influence quantities

    e. Choosing and applying appropriate reference standards
    f. Uncertainty estimation
3. Choice of the Reference
    a. Physical measurements made during analytical work
    b. Confirmation of identity
    c. Calibrations with CRMs
    d. Calibrations using other materials
    e. Calibration using reference data
4. Reporting Traceability

Analytical measurement and uncertainty

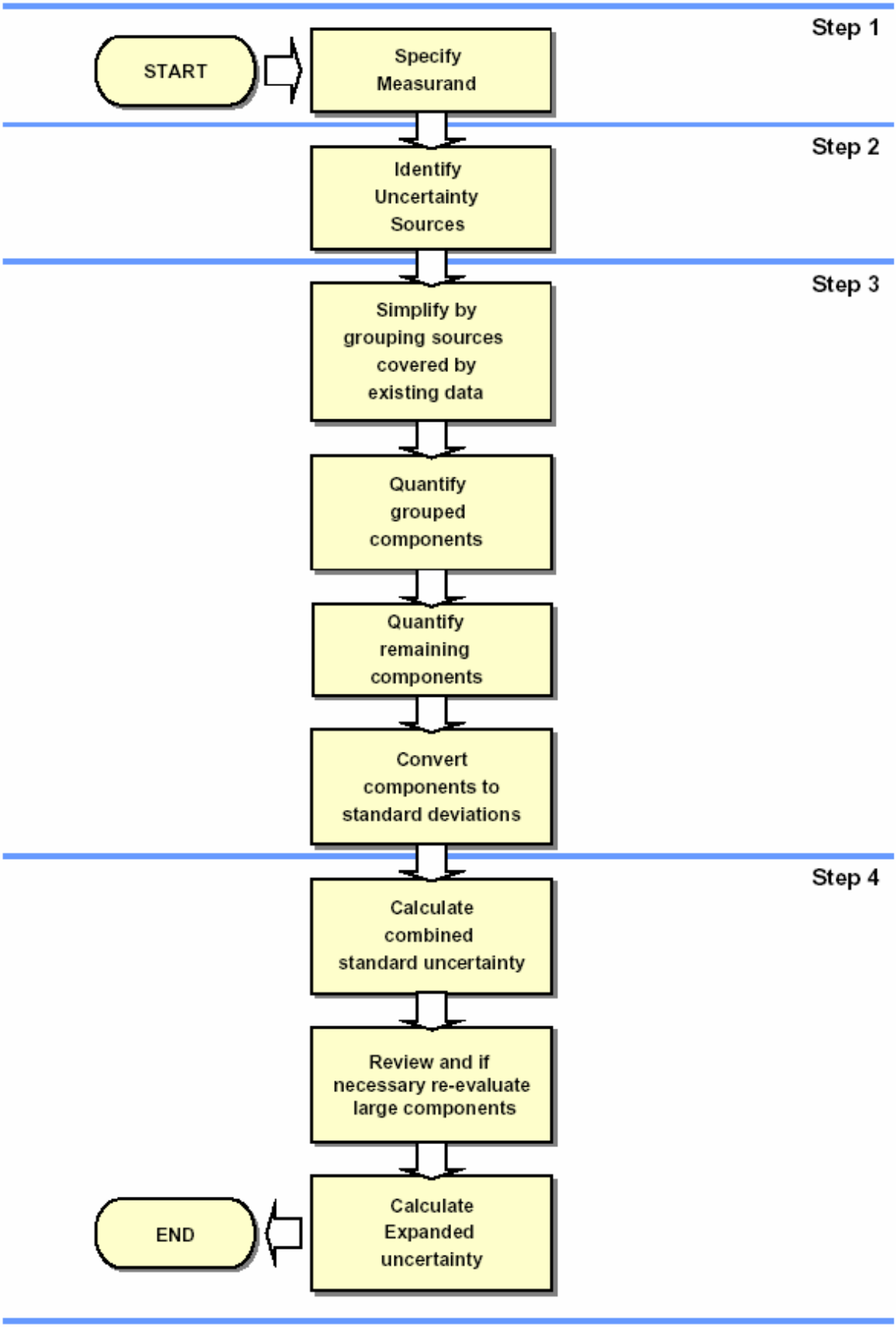
Uncertainty: “a parameter associated with the results of a measurement, that characterises the dispersion of the values that could reasonably be attributed to the measurands.”

1. Method validation
    a. Precision
    b. Bias (traceability)
    c. Linearity
    d. Detection limit
    e. Robustness (rugedness)
    f. Selectivity
2. Conduct of experimental studies of method performance (representativeness is essential)
3. Traceability
    a. Calibration of measuring equipment
    b. Measurements using Primary Methods. “A primary method of measurement is a method having the highest metrological qualities, whose operation is completely described and understood in terms of SI units and whose results are accepted without reference to a standard of the same quantity.”
    c. Measurements using a pure substance Reference Material (RM). “Material or substance one or more of whose property values are sufficiencly homogeneous and well established to be used for the calibration of apparatus, the assessment of a measurement method, or for assigning values to materials.”
    d. Measurement on a Certified Reference Material (CRM). “A CRM is RM, accompanied by a certificate, one or more of whose property values are certified by a procedure which establishes traceability to an accurate realisation of the unit in which the property is expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence.”
    e. Measurement using an accepted procedure

The process of measurement uncertainty estimation

1. Specification of the Measurand
2. Identifying Uncertainty Sources
    a. Sampling
    b. Storage conditions
    c. Instrument effects
    d. Reagent purity
    e. Assumed stoichimetry
    f. Measurement conditions
    g. Sample effects
    h. Computational effects
    i. Blank correction
    j. Operator effects
    k. Random effects
3. Quantifying Uncertainty
    a. Uncertainty evaluation procedure
        i. Reconcile the information requirements with the available data
        ii. Plan to obtain further data required
    b. Relevance of prior studies
    c. Evaluating uncertainty by quantification of individual components
    d. Closely matched CRMs
    e. Uncertainty estimation using prior collaborative method development and validation study data
    f. Uncertainty estimation using in-house development and validation studies
        i. Precision study
        ii. Bias study
    g. Evaluation of uncertainty for empirical methods
    h. Evaluation of uncertainty for ad-hoc methods
    i. Quantification of individual components
    j. Experimental estimation of individual uncertainty contributions
    k. Estimation based on other results or data
        i. PT schemes
        ii. QA data
        iii. Suppliers' information
    l. Modelling from theoretical principles
    m. Estimation based on judgement
    n. Significance of bias
4. Calculating the Combined Uncertainty
    a. Standard uncertainties (e.g., standard deviation of the mean)
    b. Combined standard uncertainty
    c. Expanded uncertainty
5. Reporting Uncertainty

Figure 1: The Uncertainty Estimation Process



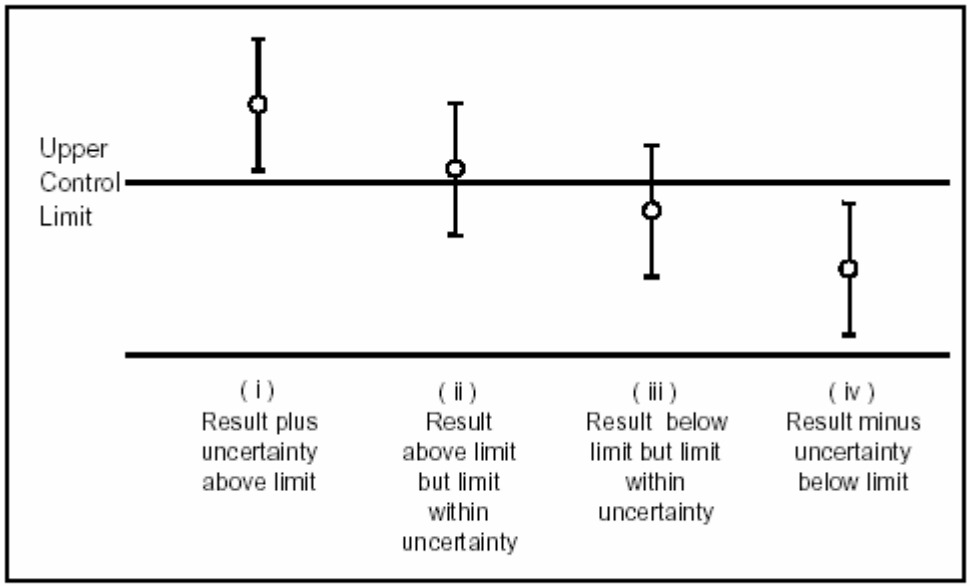


Figure 2: Uncertainty and compliance limits

Sources of uncertainty in neutron activation analysis

1. Preparation of the sample and comparator (standards, monitors)
    a. Mass determination of a sample
    b. Mass determination of comparators
    c. Mass changes of samples due to moisture uptake during weighing
    d. Concentration of comparators (standards), purity and stooichiometry of chemicals used for the preparation of standards and/or the uncertainty of k_0-values
    e. Variation of isotopic abundance
    f. Blank variation and the necessary correction (due to analyte content in an irradiation vial and/or capsule)
2. Irradiation
    a. Irradiation geometry differences
    b. Neutron self-shielding/scattering differences
    c. Irradiation time
    d. Nuclear reaction interferences
    e. Neutron spectrum variations in time and space
    f. Volatilisation losses during irradiation
3. Gamma spectrometric measurement
    a. Counting statistics
    b. Counting geometry differences
    c. Pulse-pileup losses (random coincidences)
    d. True coincidences (cascades)
    e. Dead-time effects
    f. Decay timing effects
    g. Counting time
    h. Gamma ray self-shielding
    i. Gamma-ray interferences
    j. Peak integration method
    k. Blank correction (due to counting room/shielding background)
4. Radiochemical separation
    a. Mass determination of stable carrier and/or tracer
    b. Yield determination
    c. Isotopic exchange between the radiotracer and/or stable carrier

Propagation of uncertainties

If we have a formula:

$$y = f(x)$$

then the absolute uncertainty in x is dx, the absolute uncertainty is dy and the relative uncertainty is dy/y

Uncertainties are combined in the following way:

1. Addition and subtraction: $z = x + y$ or $z = x - y$

$$s_z = \sqrt{s_x^{\,2} + s_y^{\,2}}$$

2. Multiplication and division: $z = xy$ or $z = x/y$:

$$s_z = \sqrt{(\frac{s_x}{x})^2 + (\frac{s_y}{y})^2}$$

3. Products of powers: $z = x^m y^n$

$$s_z = \sqrt{(\frac{ms_x}{x})^2 + (\frac{ns_y}{y})^2}$$

Suppose we have an implicit function of the form:

$$F(\alpha, x_1, x_2, x_3, \ldots) = 0 \qquad (1)$$

where x_1, x_2, x_3, . . .are either statistical variables (e.g. measured count rates) or fixed parameters with an associated uncertainty (e.g. nuclear data). Then the overall (total) relative uncertainty on α, as a function of the relative uncertainties on the x's, is given by:

$$s_{\alpha,T} = \left\{ \sum_j \left[Z_\alpha(x_j) s(x_j) \right]^2 \right\}^{\frac{1}{2}} \qquad (2)$$

where the uncertainty propagation factor $Z_\alpha(x_j)$ is defined as the multiplier of the relative uncertainty on x_j to obtain the associated relative uncertainty on α. When writing the relative uncertainties in terms of differentials, one obtains according to the abpve definition:

$$Z_\alpha(x_j) = \left| \frac{\frac{d\alpha}{\alpha}}{\frac{dx_j}{x_j}} \right| \tag{3}$$

where $Z_\alpha(x_j)$ denotes the partial uncertainty propagation factor for α, caused by the relative uncertainty on x_j.
Since partial derivation of the function F (1) yields

$$\frac{\partial F}{\partial \alpha} d\alpha + \frac{\partial F}{\partial x_j} dx_j = 0 \tag{4}$$

Eq. (3) becomes finally:

$$Z_\alpha(x_j) = \left| \frac{x_j}{\alpha} \frac{\frac{\partial F}{\partial x_j}}{\frac{\partial F}{\partial \alpha}} \right| \tag{5}$$

From Eq. (5) it is possible to calculate uncertainty propagation factors for the individual variables and parameters in Eq. (1). To obtain the overall uncertainty on α, these $Z_\alpha(x_j)$-factors have to be introduced in Eq. (2), together with the measured or estimated uncertainties on the x_j- parameters under consideration.

$$c_m = \frac{M_a}{N_A \theta_a \gamma_a} \frac{\left(\frac{N_p / t_c}{SDCW} \right)_a}{\left(G_{th,a} \Phi_0 \sigma_{0,a} + G_{e,a} \Phi_e I_{0,a}(\alpha) \right) \varepsilon_{p,a} Y_a}$$

$$S = 1 - e^{-\lambda t_i} \qquad D = e^{-\lambda t_d} \qquad C = (1 - e^{-\lambda t_c}) / \lambda t_c$$

$$c_m = \frac{\left(\frac{N_p / t_c}{SDCW} \right)_a}{A_{sp,n}} \cdot \frac{1}{k_{0,n}(a)} \cdot \frac{G_{th,n} f + G_{e,n} Q_{0,n}(\alpha)}{G_{th,a} f + G_{e,a} Q_{0,a}(\alpha)} \cdot \frac{\varepsilon_{p,n}}{\varepsilon_{p,a}}$$

Literature:

1. Quality Assurance for Research and Development and Non-routine Analysis, Eurachem/CITAC, 1998.
2. Harmonised Guidelines for Internal Quality Control in Analytical Chemistry Laboratories, Pure & Applied Chem., Vol. 67, No. 4, pp.649-666, 1995.
3. The Fittness for Purpose of Analytical Methods; A Laboratory Guide to Method Validation and Related Topics, Eurachem, 1998.
4. Harmonized Guidelines for Single-Laboratory Validation of Methods of Analysis, Pure & Applied Chem., Vol. 74, No. 5, pp. 835-855, 2002.
5. Traceability in Chemical Measurement, Eurachem/CITAC Guide, 2003.
6. Quantifying Uncertainty in Analytical Measurement, Eurachem/CITAC Guide, 2000.
7. Quantifying Uncertainty in Nuclear Analytical Measurements, IAEA-TECDOC-1401, 2004.