1989-2019 Eurachem

A focus for analytical chemistry in Europe

The use of reference materials in demonstrating metrological traceability – Reference to ISO 17034

Marina Patriarca

Istituto Superiore di Sanità, Rome, Italy

Laboratory Accreditation
A TWO-DAY TRAINING COURSE - CRITICAL ISSUES OF THE ACCREDITATION STANDARDS - ISO/IEC 17025:2017 AND ISO 15189:2012
Nicosia (Cyprus), 21st - 22nd February 2019

Aim of the training

To give you an overview of

- What is metrological traceability and why we need it?
- What guidance is available?
- The International Metrological Structure
- What is the role of reference materials?
- How is metrological traceability achieved?
- How to choose appropriate CRMs?

Requirements for the quality of (analytical) measurements

to produce results:

- **comparable** over places
- **comparable** over time
- fit for the purpose,
  e.g.
  for **comparison**
  with limit values
  or reference ranges

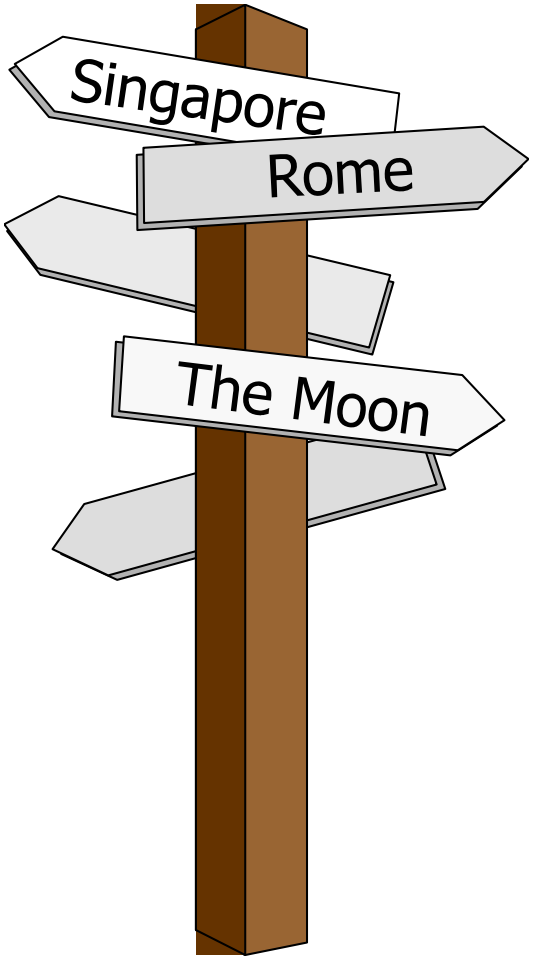
Comparable measurement results

Measurement results (metrologically) **traceable** to the same **reference**

Quantities of the same kind (e.g. lengths)

- Same reference, e.g. the metre
- Values and uncertainties not necessarily of the same magnitude

(VIM 2.46)



Eurachem 1989-2019 30
A focus for analytical chemistry in Europe

ISO/IEC 17025:2017 - A New Accreditation Standard

Requirements for competent laboratories

New emphasis on metrological traceability!

Contents

2017 saw the publi… of a new version… ISO/IEC 1702… …eral requireme… …e compet… …esting and calib… …oratories. A… …ier things, the …andard has a …stantially revised …ructure, including different management system options. There is a new emphasis on "risks and opportunities", clearer reference to sampling activities, new requirements around conformity assessment and a new emphasis on metrological traceability.

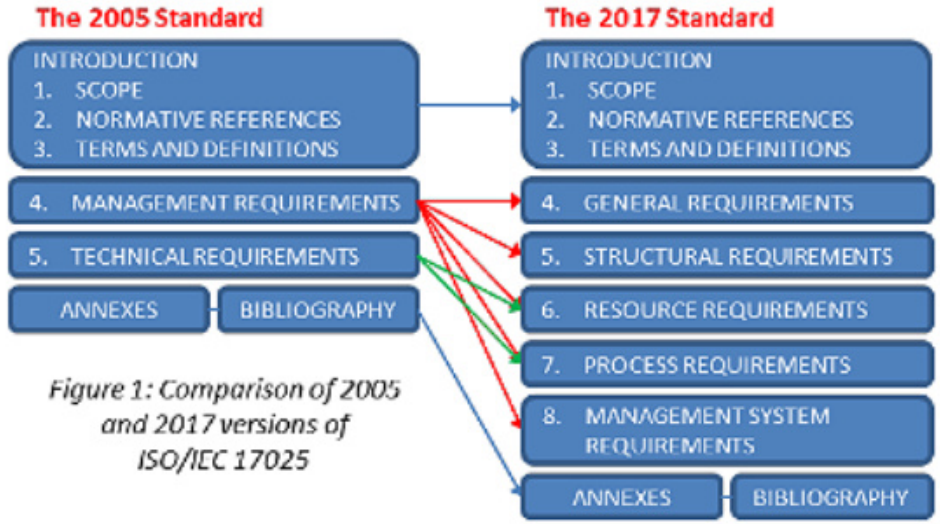


Figure 1: Comparison of 2005 and 2017 versions of ISO/IEC 17025

Requirements – ISO/IEC 17025

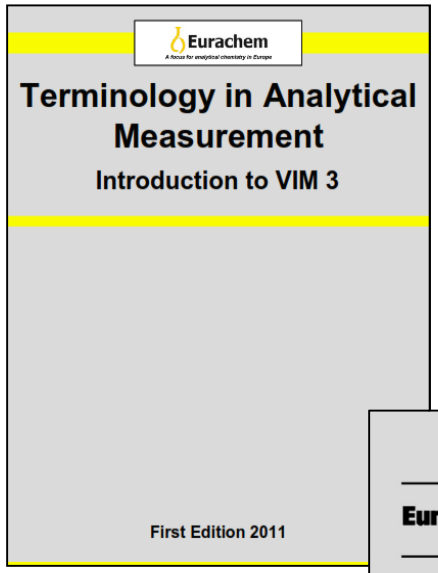
- **6.5.1** The laboratory shall establish and maintain **metrological traceability** of its measurement results by means of a documented unbroken chain of calibrations, each contributing to the measurement uncertainty, linking them to an appropriate reference.

1989-2019 Eurachem

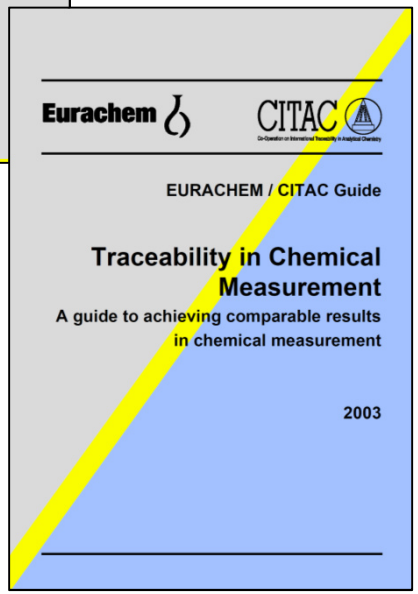
A focus for analytical chemistry in Europe

Relevant Guidance

Revision due 2019



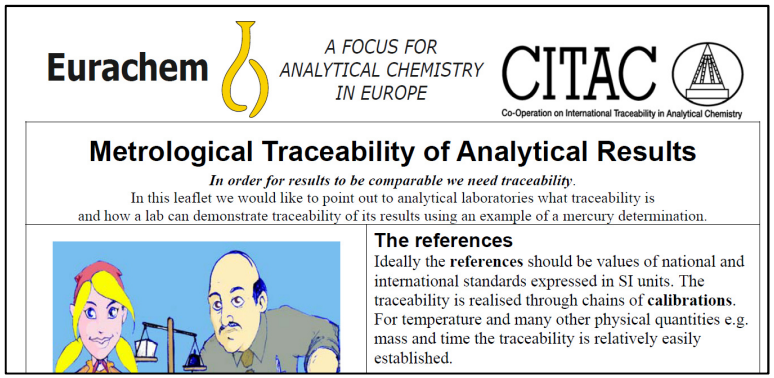
Revision due 2019



Pure Appl. Chem., Vol. 83, No. 10, pp. 1873–1935, 2011.
doi:10.1351/PAC-REP-07-09-39

Metrological traceability of measurement results in chemistry: Concepts and implementation (IUPAC Technical Report)*

Paul De Bièvre[1,‡], René Dybkaer[2], Aleš Fajgelj[3], and D. Brynn Hibbert[4]



Definitions

Metrological 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.

(VIM3 - 2.41)

Reference

A reference can be

a measurement unit,

a measurement procedure,

a reference material,

or a combination of such.

1989-2019 Eurachem

A focus for analytical chemistry in Europe

30

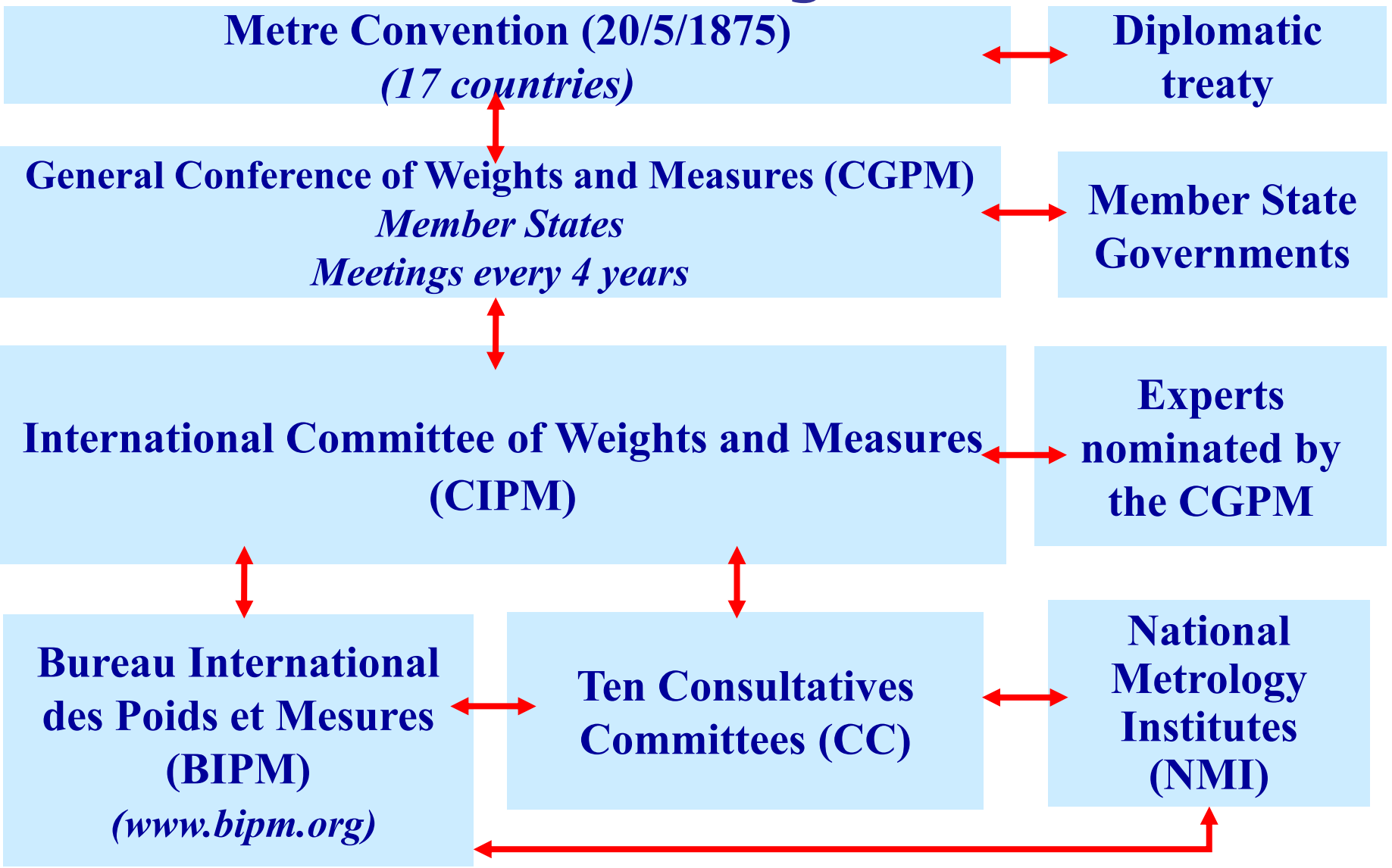
Common references

1989-2019 Eurachem

A focus for analytical chemistry in Europe

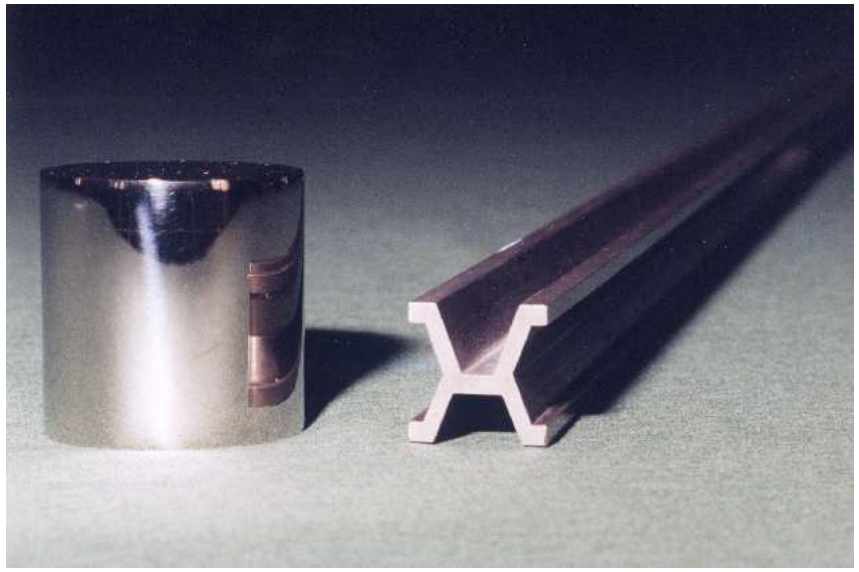
Bratislava (Slovakia), Town Hall

The International Metrological Structure



Measurement unit (VIM 1.9)

real scalar quantity, defined and adopted by convention, with which any other quantity of the same kind can be compared to express the ratio of the two quantities as a number



Redefinition of the SI

International System
Base quantities and units

Quantity	Unit
Length	metre (m)
Mass	kilogram (kg)
Time	second (s)
Electric current	ampere (A)
Thermodynamic temperature	kelvin (K)
Amount of substance	mole (mol)
Luminous Intensity	candela (cd)

EC Directive 80/181 related to measurement units

Measurement standard
(VIM3, 5.1)

- realization of the definition of a given quantity
- stated quantity value
- associated measurement uncertainty
- to be used as a reference

EXAMPLES

- mass measurement standard of 1 kg and standard measurement uncertainty of 3 µg
- hydrogen reference electrode at 7.072 pH units and standard measurement uncertainty of 0.006 pH units
- Human blood certified reference material containing 124 µg L^{-1} Pb and standard measurement uncertainty of 2 µg L^{-1} Pb

RMs and CRMs

Reference material – RM (VIM3, 5.13)

- sufficiently homogeneous and stable properties
- established to be fit for its intended use

Certified reference material – CRM (VIM3, 5.14)

- Specified property values, uncertainties and traceabilities
- Obtained using valid procedures
- Fully documented
- Issued by an authoritative body

CRMs are special types of measurement standards

1989-2019 Eurachem
A focus for analytical chemistry in Europe

Types of RMs

- Pure substances for calibration
- Pure substances for matrix matching
- Matrix CRM
- Physico-chemical standards

Matrix reference material

Material that is characteristic of a real sample

EXAMPLE Soil, drinking water, metal alloys, blood.

Note 1: may be obtained directly from biological, environmental or industrial sources.

Note 2 : may also be prepared by spiking the component(s) of interest into an existing material.

Note 3: A chemical substance dissolved in a pure solvent is not a matrix material.

Note 4: intended to be used in conjunction with the analysis of real samples of the same or a similar matrix.

ISO GUIDE 30:2015 2.1.4

(Measurement) procedure

- detailed description of a measurement

  e.g. preparation of working solutions in the laboratory

  – Must guarantee that the expected values are achieved

  – Appropriate equipment

  – Trained staff

- Comparability:

  – only if the procedures are strictly followed

  – Traceability: to the CRM, the equipment used, the procedure

Measurement procedure

detailed description of a measurement

Extractable fat in a sample of meat

The amount of extracted fat
depends on the solvent used, etc.

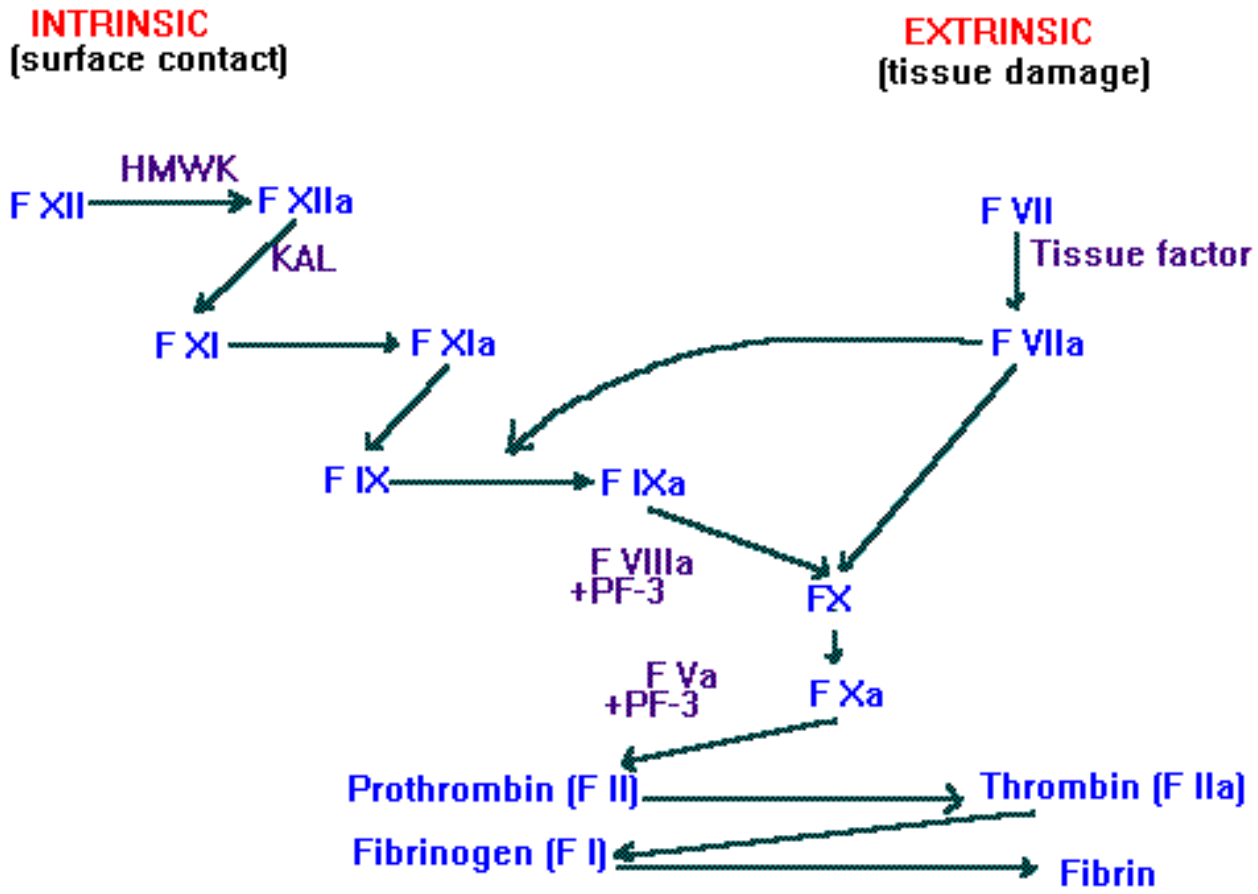
Empirical measurement procedure (standard method)

'Operationally defined' measurand

Comparability:
only if the agreed measurement procedure is strictly followed

Traceability: to the measurement procedure

Reference materials as a reference



No definite chemical structure

No agreed measurement procedure

Reference materials as a reference

WHO 1st INTERNATIONAL STANDARD FOR FACTOR VII CONCENTRATE NIBSC code: 97/592

- Ampoules containing 1 ml aliquots of a human plasma derived FVII concentrate, freeze-dried
- established by the Expert Committee on Biological Standardisation of the WHO in October 1998
- assigned activity for use with both one-stage clotting and chromogenic assay methods is 6.3 International Units per ampoule

Comparability:
only if the measurement results are obtained by direct comparison with this International Standard

Traceability: to the reference material itself

Ensuring MT to the SI

a. calibration provided by a competent laboratory
b. certified values of **certified reference materials** provided by a competent producer with stated metrological traceability to the SI
c. direct realization of the SI units ensured by comparison, directly or indirectly, with national or international standards.

ISO/IEC 17025

Ensuring MT to other appropriate references

When MT to the SI units is not technically possible, appropriate references can be, e.g.

a) **certified values of certified reference materials** provided by a competent producer;

b) **results of reference measurement procedures, specified methods or consensus standards** that are clearly described and accepted as providing measurement results fit for their intended use and ensured by suitable comparison.

ISO/IEC 17025

Steps to establish MT

Considering, and then ensuring, the following:

a) the specification of the **measurand**

b) a **documented unbroken chain of calibrations** going back to stated and **appropriate references**;

c) evaluation of measurement uncertainty for each step in the traceability chain according to agreed methods;

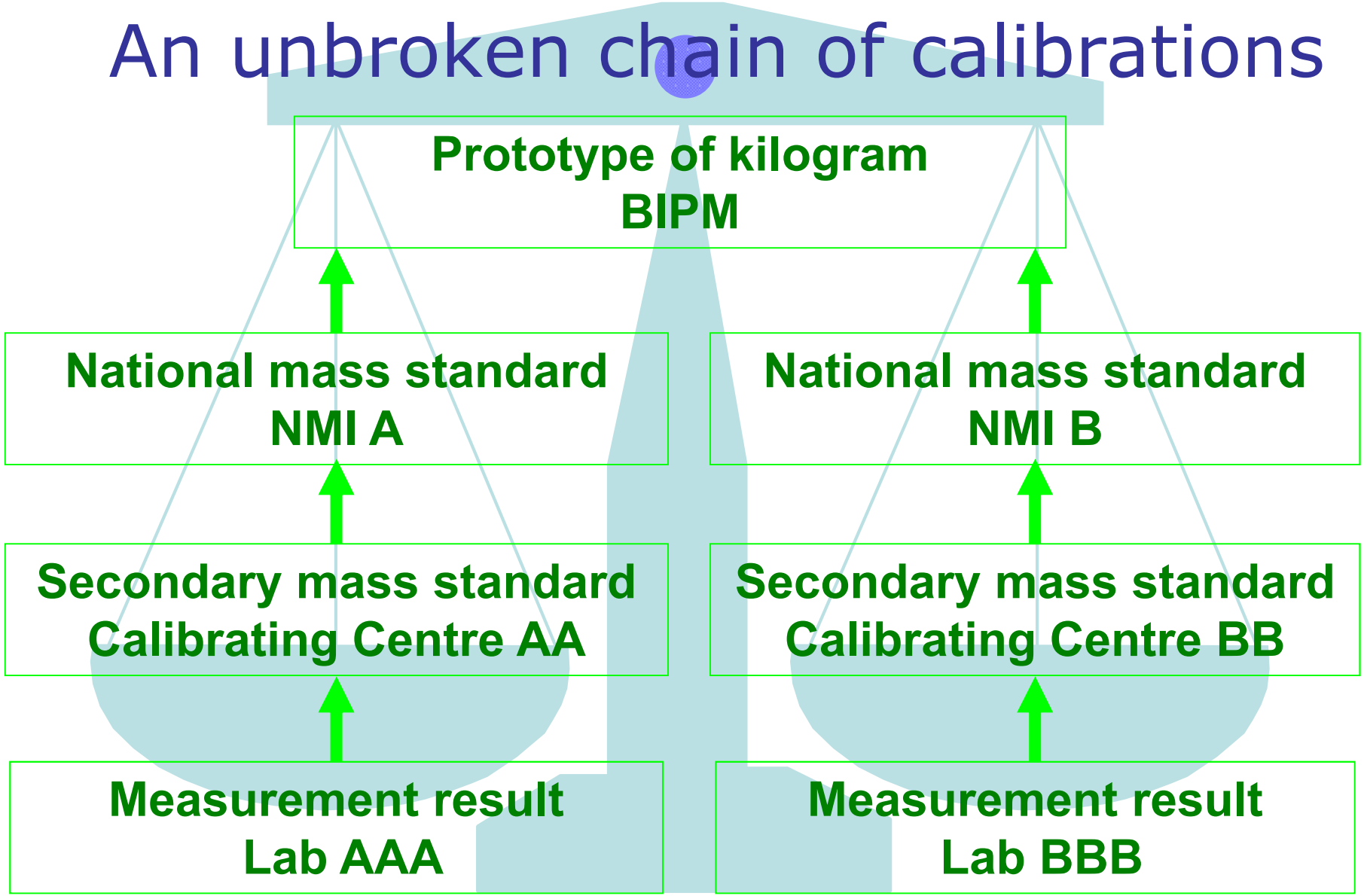
d) each step of the chain is performed in accordance with **appropriate methods**, and the measurement results and their uncertainties are **recorded**;

e) the laboratories performing one or more steps in the chain supply **evidence for their technical competence**

1989-2019 Eurachem

A focus for analytical chemistry in Europe

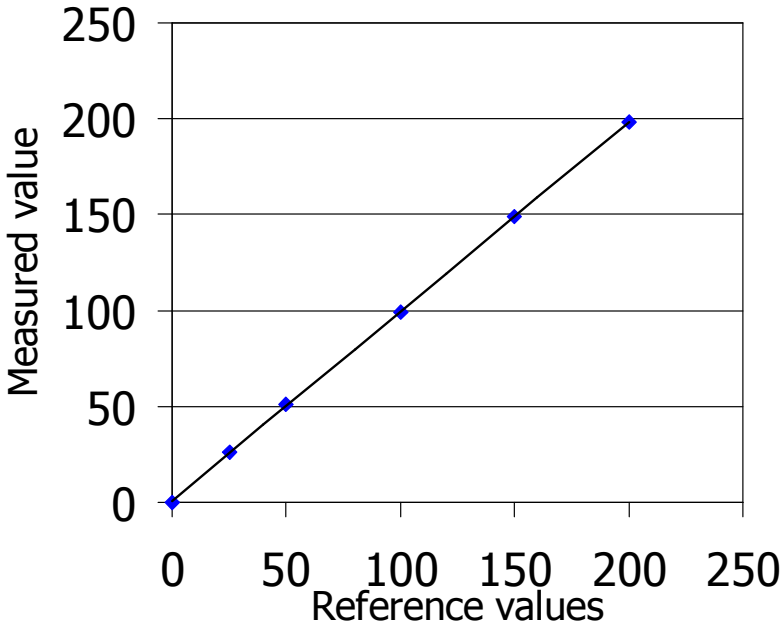
An unbroken chain of calibrations



Calibration (VIM 2.39)

- to establish a relation between the reference values and corresponding signals taking into measurement uncertainties

- to use this information to obtain a measurement result from a signal



All equipment which may have a significant effect on the accuracy or validity of the measurement result

shall be calibrated before being put into service

Calibration: what is needed

Requirements

Competent personnel / organizations

Technically valid procedures

Traceable measurement standards:

For both direct and additional measurements

Measurement uncertainty

Calibration of analytical instruments (part of the test method)

- Relationship between known amounts of the substance of interest and the instrument signal

  – Other instrument characteristics (e.g. accuracy of absorbance, repeatability, etc) may need to be included as part of the instrument qualification and metrological confirmation

Calibration uncertainty

- Over the working range
- Part of the method validation
- Data: At least 6 levels, starting from 0, each analysed at least 3 times
- Calculation: linear regression
- To be reassessed at regular intervals
- References: ISO 11095, Eurachem Guide QUAM

1989-2019 Eurachem

A focus for analytical chemistry in Europe

Uncertainty of linear calibration: Pb in water by ICP-MS

Point	Conc. µg/L	Area, yq Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Mean <Yq>	u(yq)	u(yq)/<Yq> %
q0	0,00	0,0000	0,0000	0,0000	0,0000	0,0000				0,0000	0,00000	
q1	1,00	0,4150	0,4220	0,4170	0,4240	0,4240				0,4204	0,00416	0,99%
q2	2,00	0,8010	0,7950	0,8120	0,8060	0,8000				0,8028	0,00646	0,80%
q3	5,00	1,9260	1,9820	1,9640	1,9940	1,9610				1,9654	0,02582	1,31%
q4	8,00	3,0830	3,2190	3,1890	3,1640	3,1520				3,1614	0,05080	1,61%
q5	10,00	3,9190	3,9520	3,8890	3,9510	3,9520				3,9326	0,02818	0,72%
Mean	5,20									2,05652		
n	5									25		

		Predicted Yq	Residuals		Sq residuals		q-<q>	$[q-<q>]^2$			
q1	1,00	0,41361	(Yqp-<Yq>) q=1	0,00679	4,6E-05		-4,2	17,64	a	0,02245	intercept
q2	2,00	0,80478	(Yqp-<Yq>) q=2	-0,00198	3,9E-06		-3,2	10,24	b	0,39117	slope
q3	5,00	1,97829	(Yqp-<Yq>) q=3	-0,01289	1,7E-04		-0,2	0,04	R^2	0,99998	
q4	8,00	3,15179	(Yqp-<Yq>) q=4	0,00961	9,2E-05		2,8	7,84	m	1	
q5	10,00	3,93413	(Yqp-<Yq>) q=5	-0,00153	2,3E-06		4,8	23,04	n	5	
Residuals sum						3,E-04		58,8			
Residuals SD					$s_{<y>/q}$	0,010177					

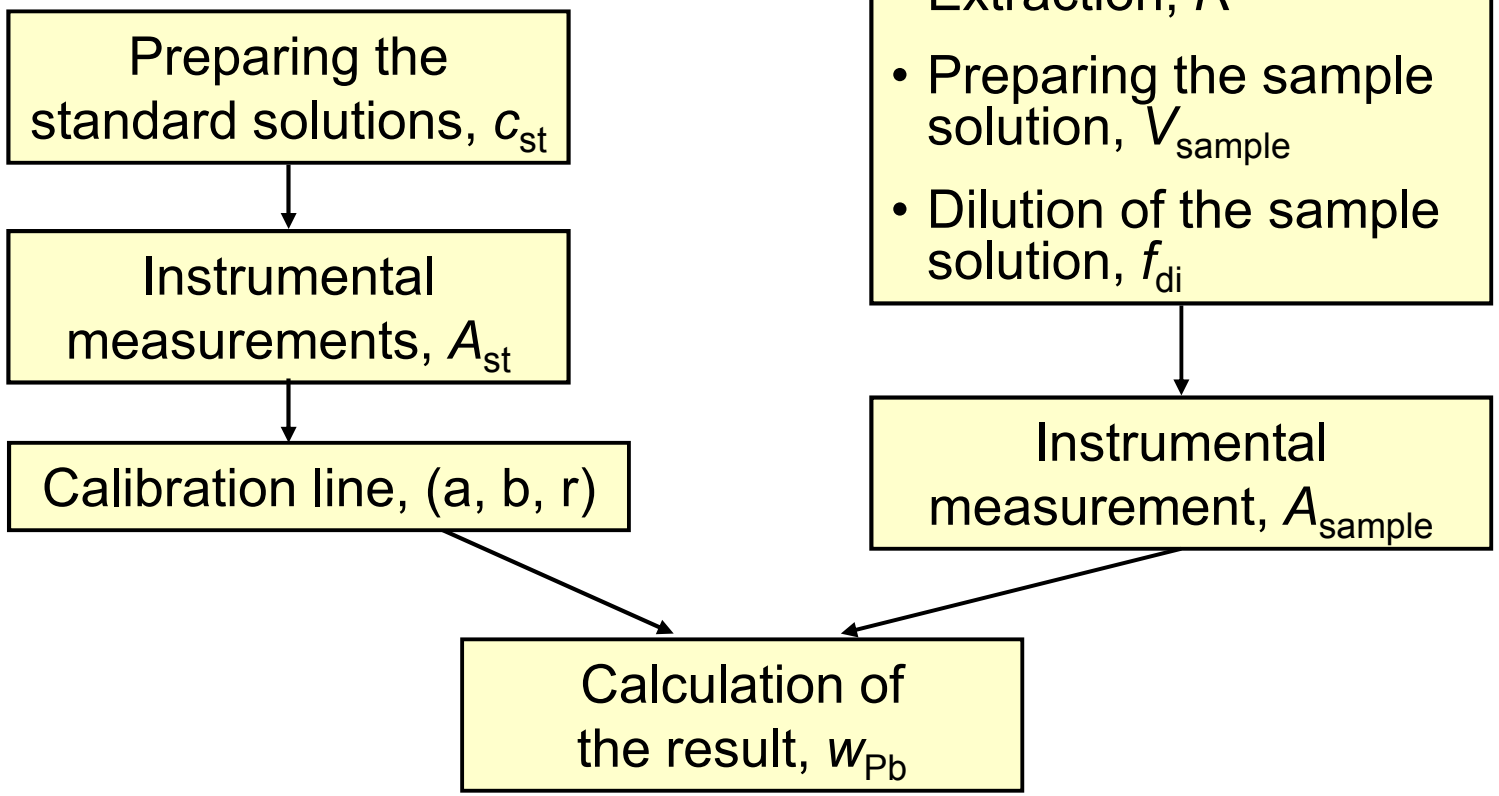
	<Yq>-Mean<Yq>^2				u	u.m.
q1	2,7E+00	0,3	1,2	u_{q1}	0,032	µg/L
q2	1,6E+00	0,2	1,2	u_{q2}	0,031	µg/L
q3	8,3E-03	0,0	1,1	u_{q3}	0,029	µg/L
q4	1,2E+00	0,1	1,2	u_{q4}	0,030	µg/L
q5	3,5E+00	0,4	1,3	u_{q5}	0,033	µg/L

Blank and five standard solutions prepared from a CRM
Each analysed 5 times

Calculations according to EURACHEM / CITAC Guide QUAM

Traceability in analytical measurement

Determination of lead in soil by flame atomic absorption spectrometry

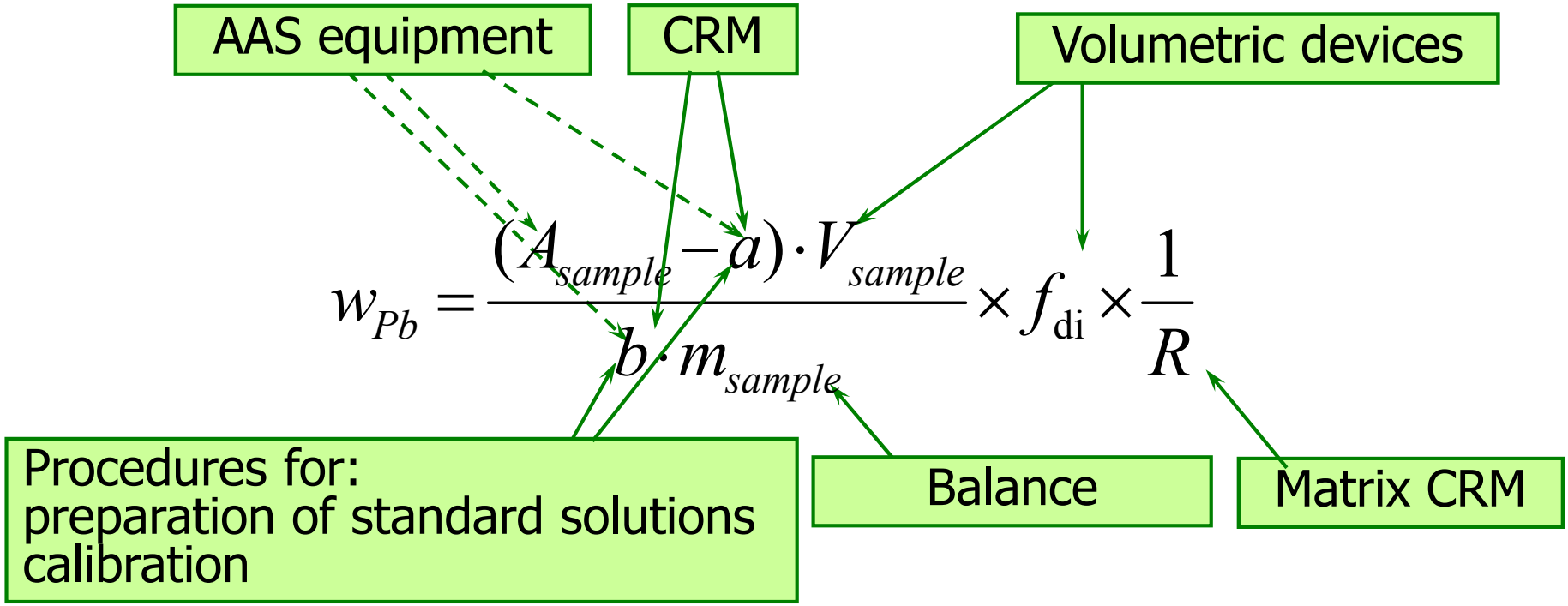


Model equation

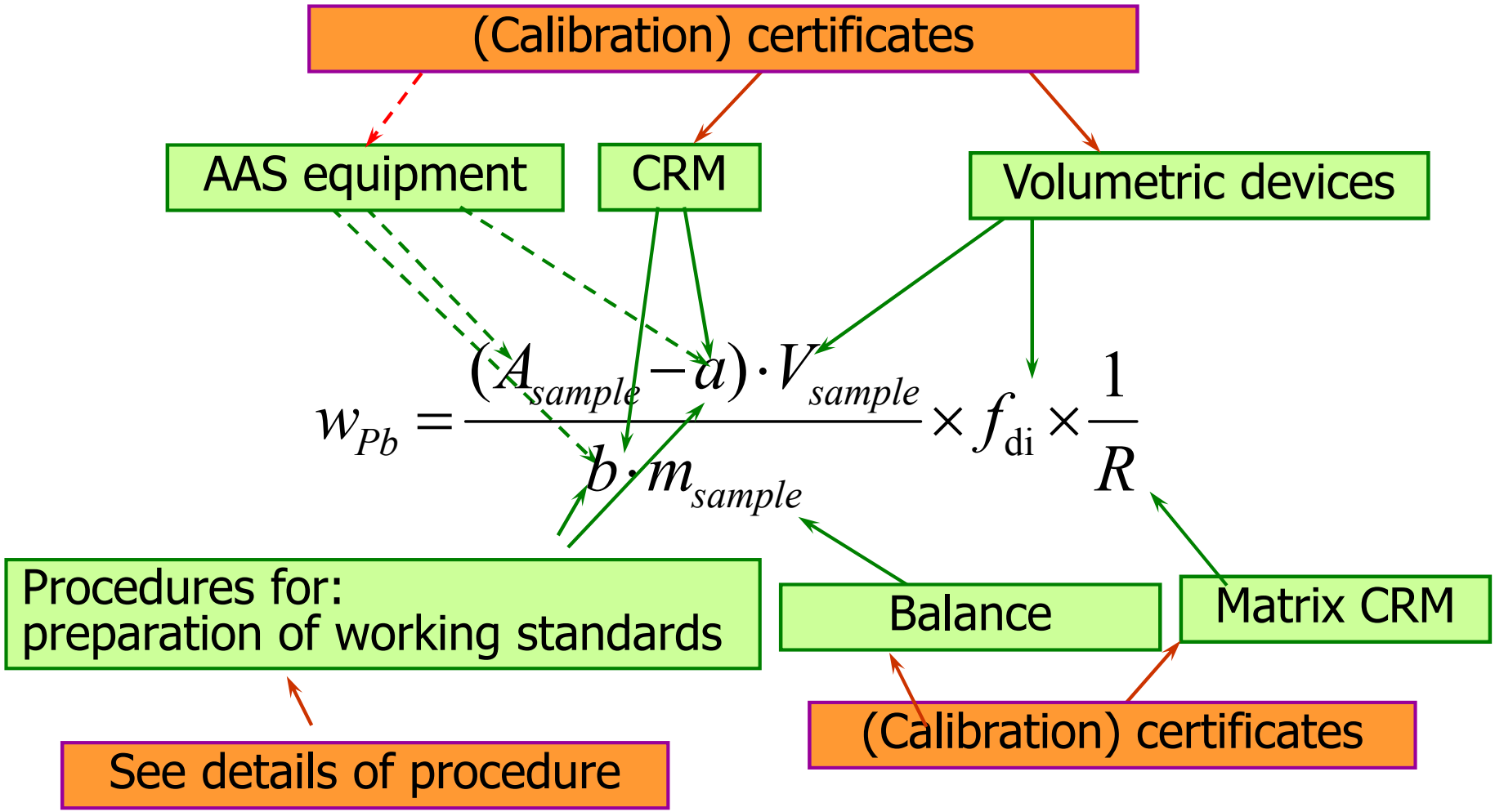
$$w_{Pb} = \frac{(A_{sample} - a) \cdot V_{sample}}{b \cdot m_{sample}} \times f_{\mathrm{di}} \times \frac{1}{R}$$

w_{Pb}	*lead mass fraction of the sample* (mg g^{-1})
A_{sample}	*absorbance measured for the sample solution* (Abs units)
a	*intercept of the calibration line* (Abs units)
b	*slope of the calibration line* (Abs units mg^{-1} L)
V_{sample}	*volume of the sample solution* (L)
m	*mass of the sample* (g)
f_{di}	*dilution factor* (unit: 1);
R	*recovery factor (*unit: 1)

Traceability for input quantities



Traceability for input quantities



Assessing CRMs

Requirements for RM Producers

- ISO Guide 30:2015. Reference materials -- Selected terms and definitions
- ISO Guide 31:2015. Reference materials -- Contents of certificates, labels and accompanying documentation
- ISO Guide 33:2015. Reference materials -- Good practice in using reference materials.
- **ISO 17034:2016. General requirements for the competence of reference material producers**
- ISO Guide 35:2017. Reference materials -- Guidance for characterization and assessment of homogeneity and stability.

Technical requirements for RMPs
(selected)

- Production planning
- Production control
- Material handling and storage
- Material processing
- Measurement procedures
- Measuring equipment
- Data integrity and evaluation
- Metrological traceability of certified values
- Assessment of homogeneity
- Assessment and monitoring of stability
- Characterization
- Assignment of property values and their uncertainties
- RM documents and labels
- Distribution services

1989-2019 Eurachem

A focus for analytical chemistry in Europe

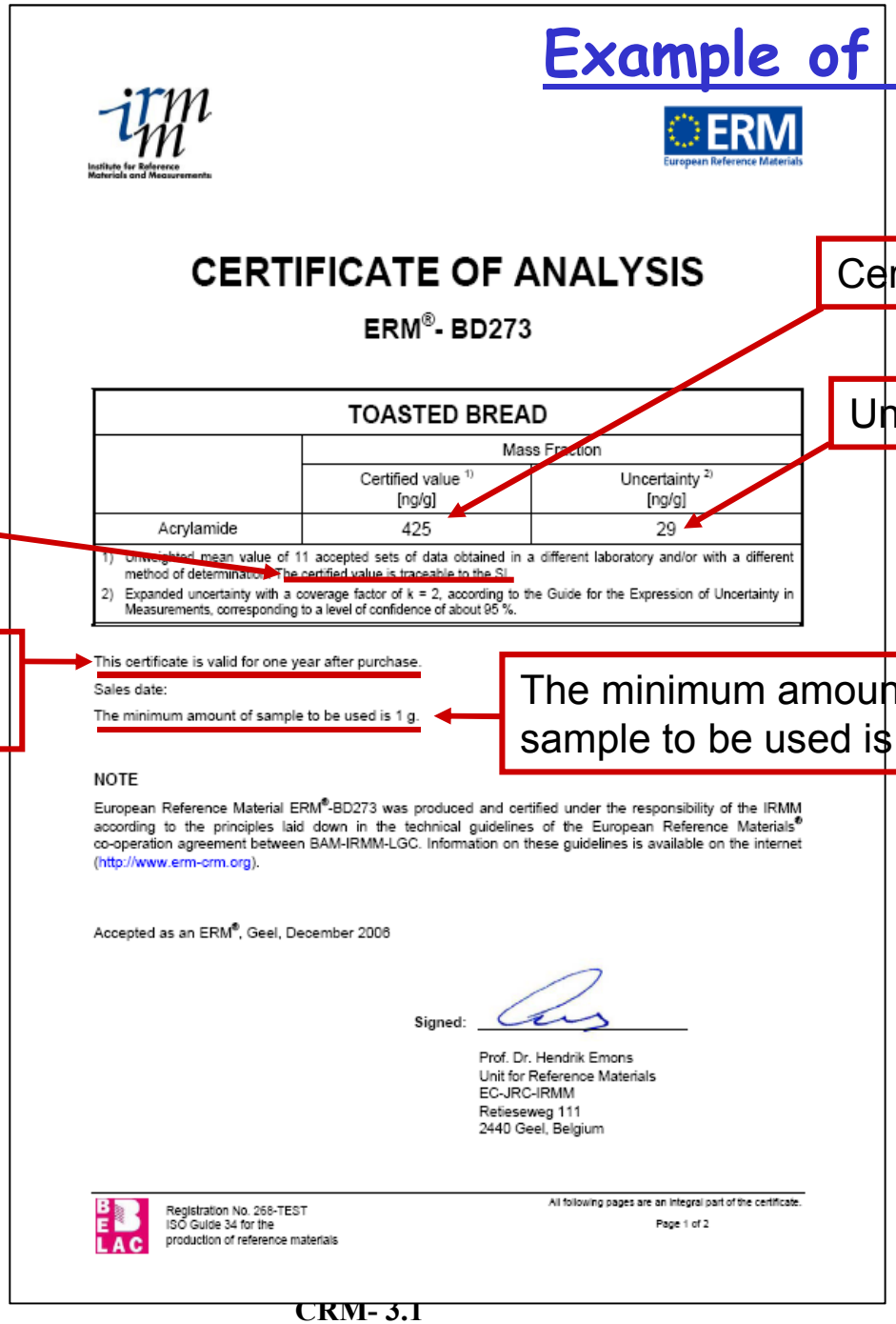
CRM CHARACTERIZATION

- a **single reference measurement procedure** in a single laboratory
- **two or more methods** of demonstrable accuracy in one or more competent laboratories
- a **method-specific approach** giving only method-specific assessed property values, using a network of competent laboratories
- **value transfer** from an RM to a closely matched candidate RM (single measurement procedure performed by one laboratory)
- characterization based on **mass or volume of ingredients used** in the preparation of the RM

ISO/IEC 17034

TrainMiC
Training in Metrology in Chemistry

Example of certificate



irmm
Institute for Reference Materials and Measurements

ERM
European Reference Materials

CERTIFICATE OF ANALYSIS

ERM®- BD273

TOASTED BREAD		
	Mass Fraction	
	Certified value [1] [ng/g]	Uncertainty [2] [ng/g]
Acrylamide	425	29

1) Unweighted mean value of 11 accepted sets of data obtained in a different laboratory and/or with a different method of determination. The certified value is traceable to the SI.
2) Expanded uncertainty with a coverage factor of k = 2, according to the Guide for the Expression of Uncertainty in Measurements, corresponding to a level of confidence of about 95 %.

This certificate is valid for one year after purchase.
Sales date:
The minimum amount of sample to be used is 1 g.

NOTE

European Reference Material ERM®-BD273 was produced and certified under the responsibility of the IRMM according to the principles laid down in the technical guidelines of the European Reference Materials® co-operation agreement between BAM-IRMM-LGC. Information on these guidelines is available on the internet (http://www.erm-crm.org).

Accepted as an ERM®, Geel, December 2006

Signed:

Prof. Dr. Hendrik Emons
Unit for Reference Materials
EC-JRC-IRMM
Retieseweg 111
2440 Geel, Belgium

BELAC Registration No. 268-TEST
ISO Guide 34 for the production of reference materials

All following pages are an integral part of the certificate.
Page 1 of 2

Certified value

Uncertainty

The certified value is traceable to the SI

The certificate is valid for one year after purchase

The minimum amount of sample to be used is 1 g

TrainMiC
Training in Metrology in Chemistry

Example of certificate

DESCRIPTION OF THE SAMPLE

ANALYTICAL METHODS USED FOR CERTIFICATION

LABORATORIES USED FOR CERTIFICATION

INSTRUCTION FOR USE
… intended for method validation and quality control purposes.

DESCRIPTION OF THE SAMPLE

The matrix material ERM-BD273, consists of 30 g of toasted bread powder of particle size smaller than 500 µm, stored in amber glass bottles under inert atmosphere and kept at a temperature of - 20 °C until delivery.

ANALYTICAL METHODS USED FOR CERTIFICATION

The participant laboratories applied validated methodologies of their own choice which in all cases included a mass spectrometric detection, coupled to different separation techniques, either gas chromatography or high performance liquid chromatography. Chromatographic columns employed differed in their dimensions and stationary phases. Diverse sample extraction strategies and clean up procedures were used and in some cases derivatisation by bromination was applied. Quantification was performed by mass spectrometry in the presence of an isotopically labelled standard, either deuterated acrylamide or $^{13}C_3$ acrylamide, employing instrumental conditions and focusing on identification and quantification ions which varied from one method to the other.

PARTICIPANTS

- Eurofins, Wiertz-Eggert-Jörissen, Hamburg (DE)
- Lebensmittelversuchsanstalt, Wien (AT)
- VWA Keuringsdienst van Waren, Eindhoven (NL)
- Lebensmittelchemisches Institut, Köln (DE)
- Kantonales Labor, Zürich (CH)
- Dublin Public Analyst Laboratory, Dublin (IE)
- National Food Administration, Uppsala (SE)
- German Research Centre of Food Chemistry, Garching (DE)
- Nestle Research Center, Lausanne (CH)
- General Chemical State Laboratory, Food and Environment Division, Athens (EL)
- Chemisches und Veterinäruntersuchungsamt, Stuttgart (DE)
- Chemisches und Veterinäruntersuchungsamt, Sigmaringen (DE)
- European Commission, Joint Research Centre, Institute for Reference Materials and Measurements, Geel (BE)
- Bundesanstalt für Materialforschung und –prüfung, Berlin (DE)

The German Research Centre of Food Chemistry contributed to the material characterisation with three different methods, each of them having a different laboratory code assigned.

SAFETY INFORMATION

The usual laboratory safety precautions apply.

INSTRUCTIONS FOR USE

ERM-BD273 is intended for method validation and quality control purposes. The certified value has been assigned to the material "as is", no dry mass correction has been applied. Nevertheless the water content of 2.7 ± 0.2 g/100 g has been estimated by Karl Fischer Titration (on 6 units randomly chosen).

STORAGE

Upon receipt, the unopened bottles of the material should be kept at a temperature equal to or lower than - 20 °C for long-term storage. However, the European Commission cannot be held responsible for changes that happen during storage of the material at the customer's premises, especially of opened samples.

LEGAL NOTICE

Neither IRMM, its contractors nor any person acting on their behalf:
(a) make any warranty or representation, express or implied, that the use of any information, material, apparatus, method or process disclosed in this document does not infringe any privately owned intellectual property rights; or
(b) assume any liability with respect to, or for damages resulting from, the use of any information, material, apparatus, method or process disclosed in this document save for loss or damage arising solely and directly from the negligence of IRMM.

NOTE

A detailed technical report is available on www.erm-crm.org. A paper copy can be obtained from IRMM on request.

European Commission – Joint Research Centre
Institute for Reference Materials and Measurements (IRMM)
Retieseweg 111, B - 2440 Geel (Belgium)
Telephone: +32-(0)14-571.722 - Telefax: +32-(0)14-590.40

Assess the quality of CRM

"Produced according to ISO/IEC 17034 and ISO Guide 35"

Criticalities:

Interpret traceability statements

PIG LIVER			
	Mass fraction (in reconstituted material)		Number of accepted sets of data p
	Certified value [2] [mg/kg]	Uncertainty [3] [mg/kg]	
Chlortetracycline[1]	0.58	0.11	6

Unweighted mean value of the means of p accepted sets of data, each set being obtained in a different laboratory using HPLC-UV or HPLC-FLD. The value is therefore traceable to determination by HPLC.

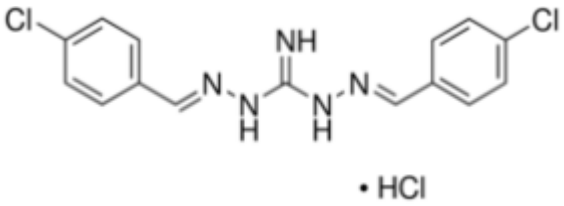
Assess the quality of CRM

"Produced according to ISO/IEC 17034 and ISO Guide 35"

Criticalities:

Many pure substances are not available as CRMs

Users need to assess their traceability, at least by comparison between different batches



33979 SIGMA-ALDRICH

Robenidine hydrochloride

VETRANAL™, analytical standard

Synonym: **1,3-Bis[(4-chlorobenzylidene)amino]guanidine monohydrochloride**

Choose CRMs fit-for-the-purpose

Assess the information available to evaluate properties of the CRM which may be critical for the intended use,

Criticalities:

- Is the CRM representative of the test samples?

A matrix CRM may provide the traceability chain for «recovery»

Recovery statements may be requested as part of the measurement result.

1989-2019 Eurachem

A focus for analytical chemistry in Europe

Can the user follow the instructions for use?

BCR® – 679

WHITE CABBAGE

INSTRUCTIONS FOR USE

The material is intended for checking the accuracy of analytical methods.

The sample can be used as it is from the bottle. Before a bottle is opened, it should be shaken for 5 min so that the material within is re-homogenised. The correction to dry mass should be made on a separate portion of 1 g that should be vacuum dried in an oven at 70 °C for 16 h until constant mass is attained. The tightly closed bottles may be kept at room temperature and should be stored in a dry empty dessicator over molecular sieve or another suitable drying agent, such as P_2O_5.

1989-2019 Eurachem
A focus for analytical chemistry in Europe

Storage and stability

- Make sure to follow the instructions for storage
- Don’t use CRMs after the expiry date
- Close CRMs tightly and store them appropriately

BCR® – 679

WHITE CABBAGE

STORAGE

The material should be stored at + 18 °C in the dark.

However, the European Commission cannot be held responsible for changes that happen during storage of the material at the customer's premises, especially of opened samples.

1989-2019 Eurachem
A focus for analytical chemistry in Europe

Choose CRMs fit-for-the-purpose

- Matrix
- Concentration range
- Traceability
- Uncertainty
- Form
- Amount
- Minimum test portion
- Corrections to be applied to results (e.g. dry mass)
- Protocol for use
- Storage conditions
- RMP compliant with ISO 17034