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Selection and use of reference materials

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Eurachem Workshop "*Complex Matrices: Applications, Laboratory Standards, and Accreditation*" - Bucharest, ROMANIA - May 26 – 27, 2025

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Outline

- The concepts of C/RMs and their role in analytical measurement
- Guidance available and in progress
- Key-elements to select a C/RM in relation to its use in your laboratory
- Existing gaps in guidance and/or understanding based on a survey among the analytical community

Many terms in common use

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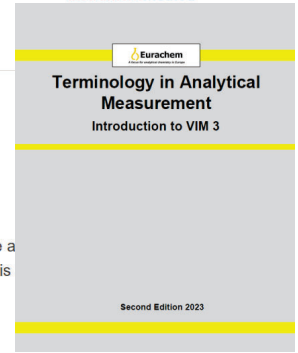
Terminology in Analytical Measurement: Introduction to VIM 3

Contents



This guide has been produced by members of the Eurachem Education and Training Working Group and others co-opted to the Project group for this task.

In the world of metrology – the science of measurement and its application – there is a language which has to be learned. The International Vocabulary of Metrology (VIM) was produced to provide a common language, primarily for physical measurements. The VIM 3 is a consistent set of concepts each described by a unique term, the 'label' of the concept. VIM 3 is applicable across all scientific disciplines thus making it relevant to those involved in performing measurements in chemistry and biology. Consistent definitions of concepts with their associated terms and symbols are essential if analysts and customers across the globe are to understand each other.

Reference Material (RM)

VIM 5.13

material, sufficiently homogeneous and stable with reference to specified properties, which has been established to be fit for its intended use in measurement or in examination of nominal properties

ISO Guide 30 2.1.1

material, sufficiently homogeneous and stable with respect to one or more specified properties, which has been established to be fit for its intended use in a measurement process

Note 2: Properties can be quantitative or qualitative, e.g. identity of substances or species.

Certified Reference Material (CRM)

VIM 5.14

reference material, accompanied by documentation issued by an authoritative body and providing one or more specified property values with associated uncertainties and traceabilities, using valid procedures

ISO Guide 30 2.1.2

reference material characterized by a metrologically valid procedure for one or more specified properties, accompanied by an RM certificate that provides the value of the specified property, its associated uncertainty, and a statement of metrological traceability

ISO Guide 30 2.1.2, Note 1

The concept of value includes a nominal property or a qualitative attribute such as identity or sequence.

Uncertainties for such attributes may be expressed as probabilities or levels of confidence.

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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.

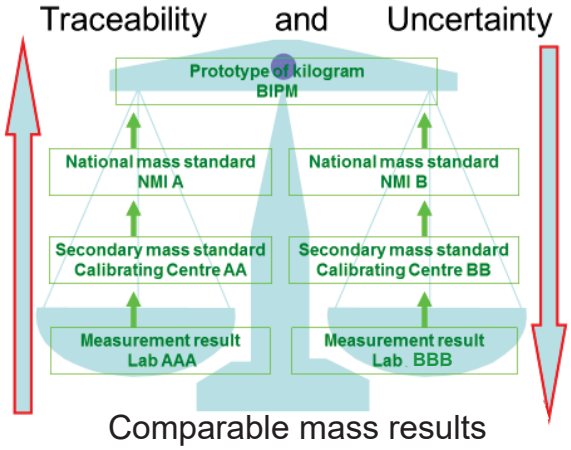
Note 3: A chemical substance dissolved in a pure solvent is not a matrix material.

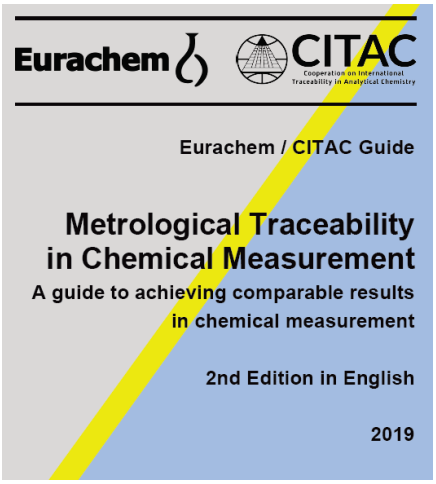
Note 4: intended to be used in conjunction with the analysis of real samples of the same or a similar matrix.

ISO GUIDE 30:2015 2.1.4

Metrological traceability (VIM3: 2.41)

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





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]

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New definitions of the SI units

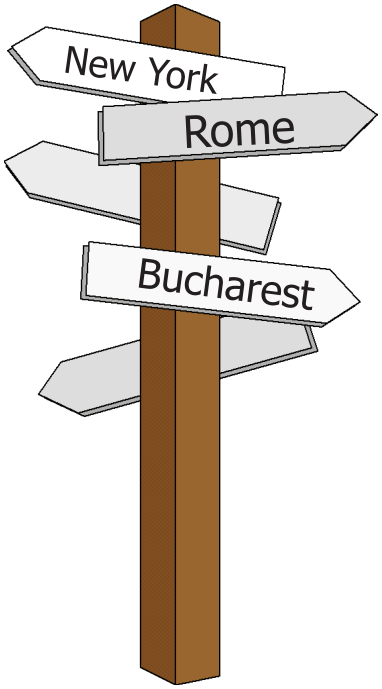
in terms of constants that describe the natural world

from May 2019 (www.bipm.org)

Why we need metrological traceability

Comparability of measurement results

VIM 2.46



To be (metrologically) traceable to the same stated reference

- Quantities of the same kind (e.g. lengths, weights, concentrations)
- Values and uncertainties not necessarily of the same order of magnitude

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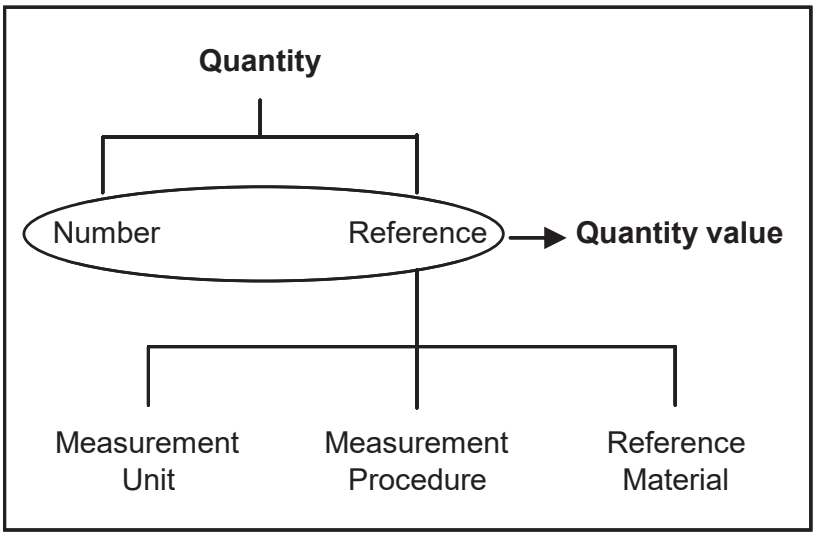
Reference

Quantity (VIM 1.1): property of a phenomenon, body, or substance, where the property has a magnitude that can be expressed as a number and **a reference**

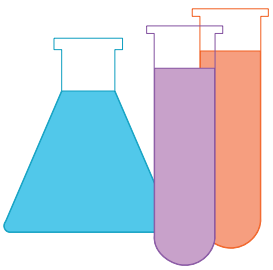


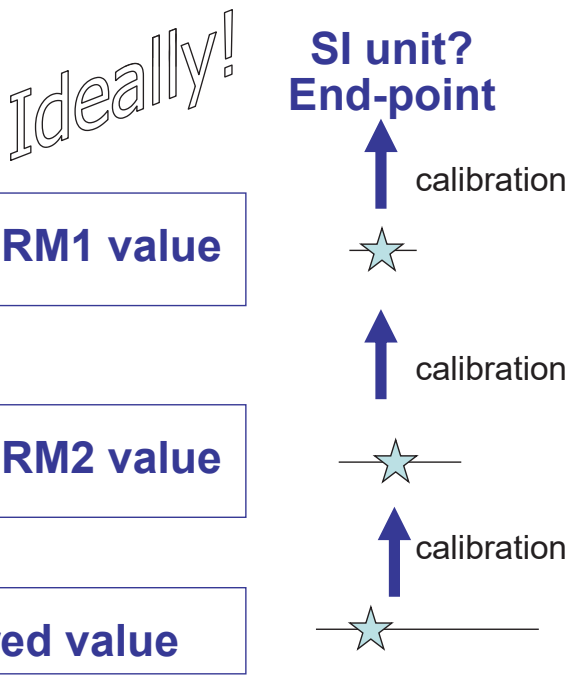
WHO International Biological Reference Preparations

- Blood coagulation factor XIII, Lyophilized, Activity 0.91 IU/ampoule; Antigen 0.93 IU/ampoule
- Blood coagulation factors II and X, concentrate, Lyophilized, FII: 9.4 IU/ampoule, FX: 8.1 IU/ampoule
- Blood coagulation factors II, VII, IX, X, Lyophilized, 0.89 IU (factor II), 0.99 IU (factor VII), 0.9 IU (factor IX), 0.89 IU (factor X) / ampoule.
- C1 esterase inhibitor, Lyophilized, 0.89 IU/ampoule

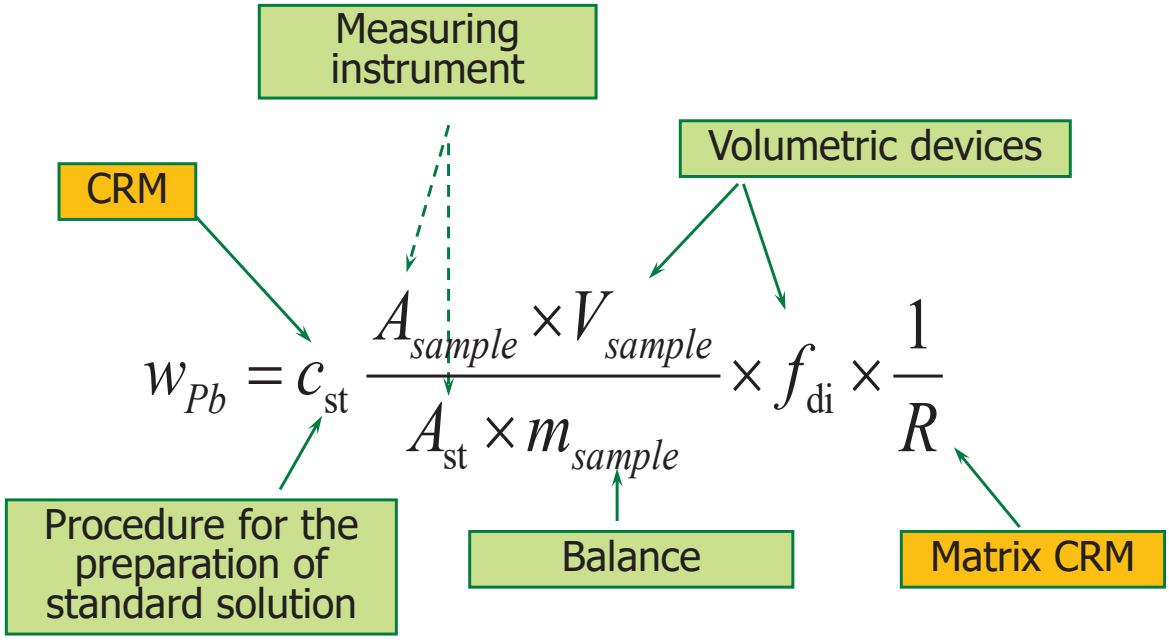
METROLOGICAL TRACEABILITY CHAIN

sequence of measurement standards and calibrations that is used to relate a measurement result to a reference (VIM, 2.42)





Metrological traceability
Role of CRMs



Guidance

- ISO/REMCO Guides
  - *Being updated to ISO standards (series 3340x)*
- ISO 17034:2016 - General requirements for the competence of reference material producers
- ISO/TC 334 – Reference materials
  - *established in 2021*
  - *revised and new guidance (series 3340x)*
  - *website: https://committee.iso.org/home/tc334*
- Eurachem Guide - Selection and use of reference materials (2002, under revision)

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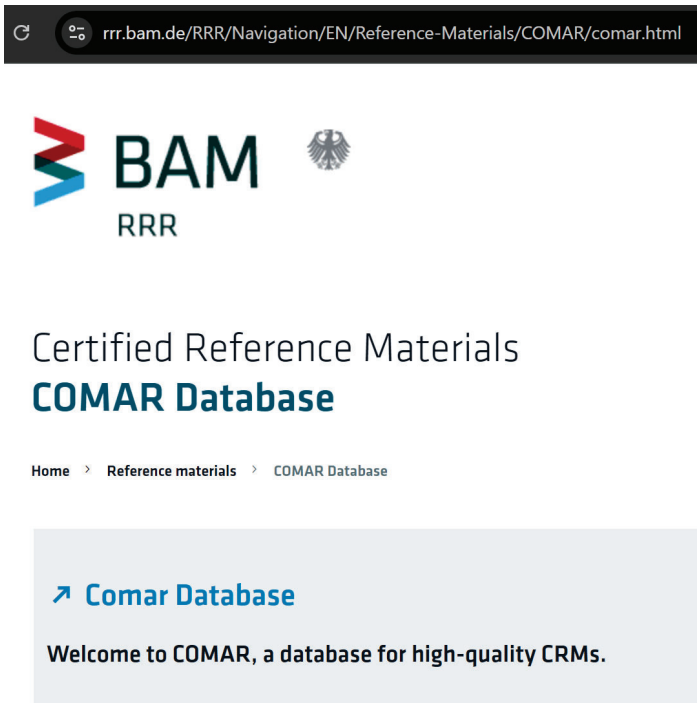
C/RMs: where to find them?



- an **internet based information service** to assist testing and analytical laboratories in finding the CRMs they need.
- maintained in a co-operation of national and international institutes.
- Free of charge, upon registration online.

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Role of C/RMs in measurement
(ISO 33403, 6.1)

- method validation
- quality control
- establishing metrological traceability
- calibration (equipment, measurement procedure)
- assigning values to other materials
- maintaining conventional scales

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ISO 33403 - Reference materials – Requirements and recommendations for use

Scope

- General recommendations on the use of RMs
- Real-world examples
- Aimed to users of RMs, but also for laboratory managers and assessors.

Contents

6 RMs and their role in measurement
7 Handling of RMs and CRMs
8 Assessment of precision
9 Bias assessment
10 Calibration
11 Assigning values to other materials
12 Conventional scales
13 Selection of RMs and CRMs

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ISO 33403 - Reference mater
Requirements and recommendatio

Scope

- General recommendations on the use of RMs

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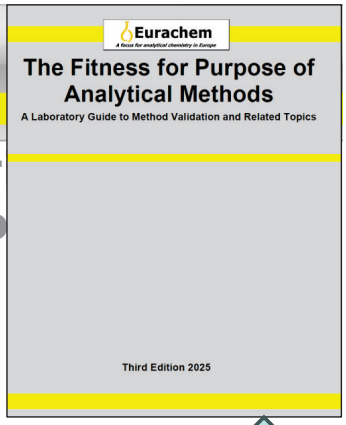

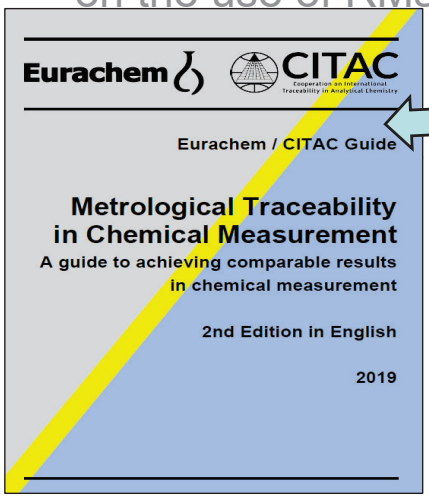

ISO 17034 - Minimum requirements

certificates and product information sheets

- description
- property, value & U
- metrological traceability statement (CRMs)
- measurement procedure for operationally defined measurands
- intended use;
- minimum sample size (whenever applicable)
- period of validity
- storage information
- instructions for handling and use
- information on commutability (where appropriate).

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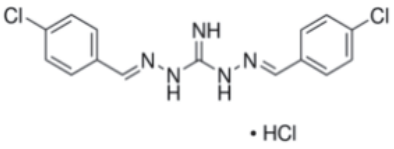
Characteristics of C/RMs	Calibration	Assessment interferences	Assessment of precision	Assessment of bias	Quality conttrol
Property of interest	Y	Y	Y	Y	Y
Matrix of interest		Y	Y	Y	Y
Property value	Y			Y	
Stated U	Y			Y	
Homogeneity	Incl. in U	Y	Y	Incl. in U	Y
Stability	Incl. in U	Y	Y	Incl. in U	Y
Metrological traceability	Y			Y	

Pure substances for calibration

- A number of pure substances are not available as CRMs

Perceived gaps in guidance:

- It is the laboratory's responsibility to define a procedure to assess that they are not significantly biased, e.g. via repeated analysis of a QC, a PT sample or a CRM.



33979 SIGMA-ALDRICH

Robenidine hydrochloride

VETRANAL™, analytical standard

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

Elements for the selection of C/RMs

- Closeness to real test samples?
  - Analyte or species?
  - Matrix
  - Level
  - Physical status
- Information provided to customers
  - Intended use?
  - Handling
  - Storage
  - Expiry date
- Additional treatments / measurements

- Quality of assigned value
  - Homogeneity
  - Minimum sample size
  - Stability
  - under transport / storage conditions
  - Metrological Traceability
  - Uncertainty
  - Commutability (if applicable)

- Availability
- Reliability of the RMP

Closeness to real test samples?

real «sample»

"Fishing" by RachelC, licensed under CC BY-NC 2.0.

C/RM

- Which property? Total content, chemical species, extractable fractions…
- Matrix? Frozen, freeze-dried, powdered, liquid…
- Level of analyte(s)?
  - Within the expected working range
  - Close to those expected in real samples
  - Ideally at both low and high levels, blanks may also be needed to assess LOD and LOQ

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C/RM fit for the purpose?

ERM®- BB422

FISH MUSCLE

Certified value for cadmium:
0.0075 mg/kg U (k=2) 0.0018 (24%)

EU Maximum Levels for Cd in fishery products: 0.050 – 0.25 mg/kg wet weight

DESCRIPTION OF THE MATERIAL

The sample consists of about 10 g of lyophilised, powdered fish muscle in a brown-glass vial with rubber insert and aluminium cap. Fish of the species *pollachius virens* (Saithe) was used for preparation of the material.

Matching C/RMs to the task

It is the user's responsibility

to justify its selection of C/RMs.

Perceived gaps in guidance:

How to deal with

- Levels too high / too low?
- Best matrix match?
- Evaluating the effect of different physical status?
- Assessing acceptable uncertainty?
- Interpreting commutability statements?
- Select appropriate C/RMs for multimatrix methods?

Did you check the instructions for use?

BCR® – 679

WHITE CABBAGE

e.g. additional treatments or measurements required

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.

Storing C/RMs at the user's premises

- Follow the instructions for storage
- Do not use CRMs beyond the expiry date on the certificate
- Make sure that the container holding the CRM is properly closed, and it is stored in an appropriate manner.

Perceived gaps in guidance:

- Setting expiry dates after opening
- Monitoring the stability of C/RMs at the user premises
- Possible uses of expired C/RMs

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Best match does not always occur

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

Requirements for analytical methods' performances – Commission Decision 657/2002/CE

- Reproducibility not exceeding the level calculated by the Horwitz Equation:

At 0.58 mg/kg ⟹ $S_{RHorwitz}$: 0.10 mg/kg

Traceability statements in CRM certificates

- required
- short and compact
- reflecting the traceability chain
- reference to other information
  - explanatory notes
  - other available documents (reports, publications)

Characterisation of CRMs – ISO 17034

- a single reference measurement procedure in a single laboratory
- two or more independent methods of demonstrable accuracy in one or more competent laboratories
- for operationally-defined measurands, a method-specific approach using a network of laboratories
- value transfer from a closely matched CRM (single measurement procedure, one laboratory)
- “formulation”, based on mass or volume of ingredients used in the preparation of the CRM

Example (A)

NIST National Institute of Standards and Technology U.S. Department of Commerce

Date of Issue: 01 April 2022

Standard Reference Material® 909c
Frozen Human Serum

Certified values traceable to the SI for amount of substance and mass determined using higher order reference measurement procedures calibrated with NIST SRMs

Method used: ID LC-MS, ID GC-MS, ID ICP-MS, ICP-OES, micro-coulometry and ion exchange-gravimetry.

Value Assignment (concentrations): weighted mean of measurement means, corrected for measured serum density.

Analytical approach for determination of each analyte provided in Appendix.

Example (B)

BCR® – 685

SKIM MILK POWDER		
	Mass fraction [1]	
	Certified value [3] [g/100 g]	Uncertainty [4] [g/100 g]
Crude protein[2] (Kjeldahl-N x 6.38)[2]	38.2	0.4
Fat	0.96	0.12

1. Results are corrected for dry mass.
2. As obtained using
    1. Crude protein content (Kjeldahl-nitrogen x 6.38): IDF standards 20-1 to 2:2001 and 3:2004, equivalent to ISO 8968-1 to 2:2001 and 3:2004
    2. Total fat content: IDF standard 9C:1987, equivalent to ISO 1736:2000
    3. Dry mass: IDF standard 26A:1993
3. Unweighted mean value of the means of accepted sets of results, each set being obtained in a different laboratory applying relevant methods of analysis standardised by IDF/ISO and AOAC.

ISO/TR 16476:2016

Reference materials — Establishing and expressing metrological traceability of quantity values assigned to reference materials

Published (Edition 1, 2016)

This publication was last reviewed and confirmed in 2023. Therefore this version remains current.

Intended primarily for RMPs,

but also helpful for users of CRMs to understand what the endpoint of their traceability chain

In doubt, check the CRM full report for more detailed information

A short survey was launched last year

- Produced by the Eurachem RMWG to support the revision of the Guide
- RMWG survey

Aim:
to listen to the analysts' experience

Main topics:

- **Existing guidance**: knowledge, availability, understanding, gaps
- **Selection and use:** practice, problems, needs

Questions 10 and 11

- which elements do you take into account to select a RM?
- which elements do you take into account to select a CRM?

Take home message…

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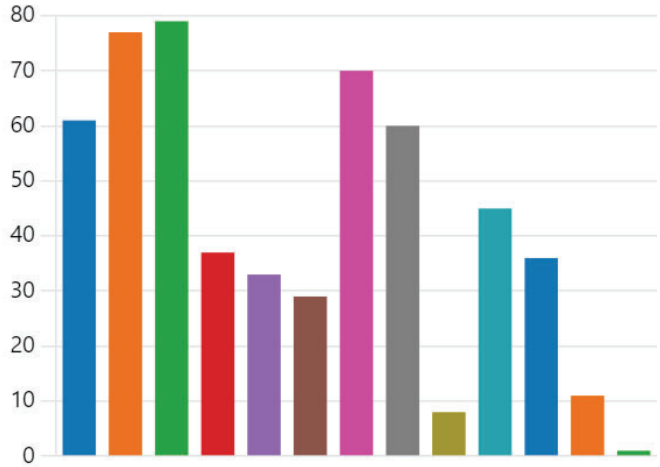
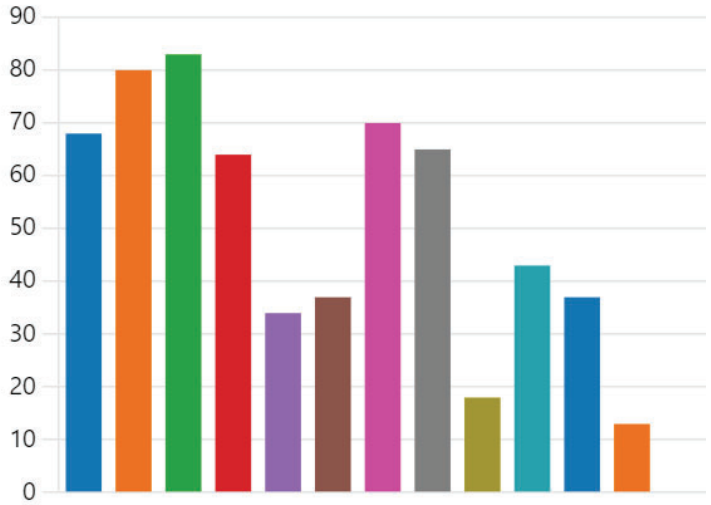
Question 10 (RM) - answers

definition of the measurand (e.g...	61
matrix	77
concentration level	79
uncertainty of the assigned value	37
physical status	33
storage conditions	29
expiry date	70
price	60
country of origin	8
availibility	45
methods used for characterisati...	36
requirements for additional mea...	11



Question 11 (CRM) - answers

definition of the measurand (e.g...	68
matrix	80
concentration level	83
uncertainty of the assigned value	64
physical status	34
storage conditions	37
expiry date	70
price	65
country of origin	18
availibility	43
methods used for characterisati...	37
requirements for additional mea...	13



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The Eurachem Guide: scope

- To provide a clear, simple and user-friendly guide, for laboratories and accreditation bodies, helping them through all the steps of selecting and using a C/RM.
- To provide basic information related the definition of C/RMs and how this applies to analytical sciences.
- To address the different roles of C/RMs and the aspects to be considered when selecting a C/RM that is fit for the purpose.
- To consider the “life after purchase” of the C/RM, including appropriate handling, storage, monitoring and possible re-use.

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Reference Materials Working Group

Joint with CITAC

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Kick-off meeting

Main current work item: Revision of the Eurachem Guide «Selection and use of reference materials»

Current membership:

- 26 Eurachem members (from EC-JRC, BG, CH, CY, CZ, DE, ES, GR, IE, IT, NL, TK, UA, UK)
- 3 CITAC Members
- 2 EA Members

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