Certified Reference Materials and Proficiency Tests: Provision, Production, and Value Assignment

Materiais de Referência Certificados e Testes de Proficiência: Disposição, Produção e Atribuição de valor

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Thank you,
to the organizing committee, the scientific committee, the promoters, sponsors, and supporters of RESAG 2015
and to you, the participants.
Topics will include:

• Global importance of chemical measurement in which we can have confidence and which can be used for the informed scientific basis of decision-making.
  • results that are consistent among different analysts, different analysts, different laboratories, and, if traceable to the SI, to different points in time and with different methods.

• Approach to achieve this
  • International infrastructure providing global linkages
  • Certified Reference Material and Proficiency Testing materials with assigned values for constituents/properties that are fit for intended use
  • Appropriately validated method for chemical/biological measurement
  • Effective Quality System to relevant Standard(s) that accounts for measurements made within a lab made between times of external checks.

• Details of Value-Assignment of CRMs and PT Materials
Need for international and/or national acceptance and confidence in measurement services

- Fair trade
- Trade agreements
  - Internal markets
  - WTO agreements
- Worldwide services
- Global issues (environmental, etc.)
- Assessment of Food Safety and Nutritional Content
- Informed Healthcare Decision-Making
- Reliability of National Security-Related Measurements and Data
- Innovation and Industrial Competitiveness
  - Whether adoption of a new innovation or method modification makes a significant difference in what is being measured?
- Industrial production (components and parts produced at another time and somewhere else on the globe must fit together)
- Accreditation agreements
- Metrological agreements
- ...

Goal: Once measured/tested, everywhere accepted
ECONOMICAL LOSSES DUE TO TEMPORAL CLOSURE OF INTERNATIONAL MARKETS TO CHILEAN EXPORTS

Due to unreliable measurements, it is likely that certain residues in foods such as antibiotics, pesticides, or heavy metals might result in higher concentration values than those established by international regulations. This might cause a temporal closure of certain destination markets. If it is assumed that, on average, such closure can last 2 months, and that re-establishment of normal trade can be achieved in 4 months, then the economic losses would be approximately:

- Temporal closure of grapes market in USA $161M
- Temporal closure of salmon market in USA $198M, Japan $176M, UE $77M
- Temporal closure of pig meat market in Japan $161M
Simplistic example of effect of bias of a PT material assigned value:

Case 1: “PT Material A” - assigned value = “true” (with insignificant uncertainty!)

Case 2: “PT Material B” with biased assigned value

Assigned value  True value

(Hidden, fraction incorrectly scored as acceptable)

What is tolerable for intended use of material?
Bias in Cholesterol Measurement Affects Medical Decision-Making

Cholesterol Frequency Distribution of >20,000 Mayo Clinic Patients (with +1%, +3% and +10% limits around 240 mg/dL criteria point)

If measurement bias were: | Positives (>240 mg/dL) per 1000 | Predicted Change in “Positives/1000”
---|---|---
-10% bias | 120 | -129
-3% bias | 203 | -46
-1% bias | 234 | -15
0% bias | 249 | +14
+1% bias | 263 | +51
+3% bias | 300 | +197
+10% bias | 446 |
Commodities

The value of a “commodity” is often determined by the amount of the major component or by the amount of various impurities in the commodity.

Examples include:

• Amount of Precious metal in metal ore determines the value

• Amount of Sulfur and Moisture in Crude Oil is inversely related to its value

+ $$$ or - $$$
Food Analysis Performance Assessment Scheme (FAPAS®) Proficiency Test 0754 Results (>70 food testing laboratories)

Tin in a frozen tomato paste

- Reference value assigned by an NMI (LGC (UK)) = 224.6 mg/kg
- Consensus value (as used in FAPAS PT evaluation) = 206 mg/kg

Effect on Rating

<table>
<thead>
<tr>
<th>Effect on Rating</th>
<th>Number of Labs.</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>'Acceptable' &gt;&gt; 'Unacceptable'</td>
<td>17</td>
<td>37</td>
</tr>
<tr>
<td>'Unacceptable'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>'Unacceptable' &gt;&gt; 'Acceptable'</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>No change to rating</td>
<td>20</td>
<td>43</td>
</tr>
</tbody>
</table>
How can we demonstrate consistency of measurement results on a global basis?
Metre Convention

Provides the framework within which the international measurement system is maintained and made available to the whole world for:

- national and international trade
- manufacturing
- human health and safety
- the protection of the environment, and
- all aspects of science and engineering

CIPM MRA

The CIPM MRA provides an open, transparent, and comprehensive system for vetting the calibration and measurement capabilities that underpin services that National Metrology Institute (NMIs) deliver to customers.
CIPM Mutual Recognition Arrangement

… was established in 1999 in response to a growing need for an open, transparent and comprehensive scheme to give users reliable quantitative information on the comparability of national metrology services and to provide the technical basis for wider agreements negotiated for international trade, commerce and regulatory affairs.

Requires:

1. Declaring and documenting calibration and measurement capabilities (CMCs)
2. Evidence of successful participation in formal, relevant international comparisons
3. Demonstration of system for assuring quality of each NMI’s measurement services
http://kcdb.bipm.org/

The BIPM key comparison database

What's new?
- Mass - EURAMET
  9 December 2015
- Mass - SIM
  9 December 2015
- All news

KCDB Newsletters
- Latest issue
- All issues
  Subscribe Unsubscribe

Related links
- KCDB Statistics
- KCDB FAQs
- KCDB Reports
- CIPM MRA
- JCRB
- Find my NMI
- Metrologia

Contact us
- BIPM_KCDB@bipm.org

In support to the Mutual Recognition Arrangement of the CIPM (CIPM MRA) of national measurement standards and of calibration and measurement certificates issued by national metrology institutes

Participants in the CIPM MRA (Appendix A)
List of national metrology institutes and designated institutes that are participant in the Arrangement.

Search comparisons:

Key and supplementary comparisons (Appendix B)
Information on CIPM (Comité International des Poids et Mesures) and RMO (Regional Metrology Organization) key and supplementary comparisons, together with results interpreted in terms of equivalence.

Search comparisons:

Calibration and Measurement Capabilities - CMCs (Appendix C)
Quantities for which calibration and measurements certificates are recognized by institutes participating in the Arrangement.

Search CMCs:

List of key comparisons (Appendix D)
All key comparisons, as defined by the Arrangement, are reported here.
Results

Laboratory individual measurements | Equivalence statements | Degrees of equivalence | Graph(s) of equivalence

MEASURAND: Amount content of Lead in natural water
NOMINAL VALUE: 63 nmol/kg

Degrees of equivalence $D_i$ and expanded uncertainty $U_i$ ($k = 2$) expressed in nmol/kg

![Graph showing data points and error bars for different laboratories: IRMM, KRISS, LGC, LNE, NIMC, NIST, NMi, NRC, PTB.](image)
### SIM.QM-S2

<table>
<thead>
<tr>
<th>Metrology area, branch</th>
<th>Amount of Substance, Inorganics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Trace elements in water</td>
</tr>
<tr>
<td>Time of measurement</td>
<td>2010</td>
</tr>
<tr>
<td>Status</td>
<td>Approved and published</td>
</tr>
</tbody>
</table>
| Reference(s)           | *Metrologia, 2012, 49, Tech. Suppl., 06004*  
                          | SIM.QM-S2 Final Report, 2011, 34 pages |
| Measurand              | Mass fractions of Cd (1 ng/g to 5 ng/g), Ni (50 ng/g to 80 ng/g), Pb (5 ng/g to 30 ng/g) and Ca (5 mg/kg to 25 mg/kg) |
| Transfer device(s)     | 100 ml bottles                  |
| Comparison type        | Supplementary comparison        |
| Consultative Committee | CCQM (Consultative Committee for Amount of Substance) |
| Conducted by           | SIM (Inter-American Metrolog)   |

**Figure 3:** Lead mass fraction as reported by the SIM.QM.S2 participants. Error bars denote the standard uncertainty as reported. The dotted red line shows the reference value. The solid red lines indicate the range of the standard uncertainty in the reference value.
Partial list of Search Results: Services of National Metrological Institutes that are published on the KCDB for Lead in Water

Warning! More than 20 summary CMCs match your selection.

**Your selection:** Chemistry, lead

21 summary CMC descriptions match your selection. Please select one or more CMCS, then click on view to access more information on the selected CMCS.

<table>
<thead>
<tr>
<th>Select</th>
<th>Analyst or component</th>
<th>Matrix or material</th>
<th>Service Provider</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>lead</td>
<td>fresh water</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>sea water</td>
<td>Australia</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>natural water, synthetic water, acid solution (up to 10 %)</td>
<td>Brazil</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>fresh water</td>
<td>Canada</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>seawater</td>
<td>Canada</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>pure water</td>
<td>European Union</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>fresh water</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>natural water</td>
<td>Germany</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>pure water</td>
<td>Germany</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>drinking water, fresh water</td>
<td>Hong Kong, China</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>river water and drinking water</td>
<td>Japan</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>fresh water</td>
<td>Mexico</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>water</td>
<td>Netherlands</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>pure water</td>
<td>Romania</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>fresh water</td>
<td>Russian Federation</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td>drinking water</td>
<td>Singapore</td>
</tr>
<tr>
<td></td>
<td>lead</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Just examples, not a complete list.
The expanded uncertainty ranges given in the following CMCs may be expressed according to two conventions. For ‘Uncertainty convention 1’, the expanded uncertainty range spans from the smallest numerical value of the uncertainty to the largest numerical value of the uncertainty found within the quantity range. For ‘Uncertainty convention 2’, the expanded uncertainty range is expressed as the uncertainty of the smallest value of the quantity to the uncertainty of the largest value of the quantity.

> Unless otherwise stated the expanded uncertainties given below correspond to $k = 2$ (level of confidence 95%)

**Water, Fresh water**

**Australia, NMIA (National Measurement Institute, Australia)**

Complete CMCs in Chemistry for Water for Australia (.pdf file)

<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th>Range of certified values in reference materials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mass fraction in mg/kg</td>
<td>Relative expanded uncertainty in %</td>
</tr>
<tr>
<td>fresh water</td>
<td>lead</td>
<td>0.01 to 100</td>
<td>1 to 4</td>
</tr>
</tbody>
</table>

Mechanism(s) for measurement service delivery: Certification service
Uncertainty convention 1.
Approved on 12 March 2013
Internal NMI service identifier: NMIA/PM1

**Water, Fresh water**

**Canada, NRC (National Research Council)**

Complete CMCs in Chemistry for Water for Canada (.pdf file)

<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th>Range of certified values in reference materials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mass fraction in ng/g</td>
<td>Absolute expanded uncertainty in ng/g</td>
</tr>
<tr>
<td>fresh water</td>
<td>lead</td>
<td>0.006 to 300</td>
<td>0.0003 to 30</td>
</tr>
</tbody>
</table>

Mechanism(s) for measurement service delivery: CRM SLRS-5
Uncertainty convention 2.
Approved on 27 March 2013
Internal NMI service identifier: NRC/TEW11

Of course, if you use these services for value assignment, you will have to agree to a price with NMI

Will value-assign customer-provided material
### Canada, NRC (National Research Council)

<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th>Range of certified values in reference materials</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Mass fraction in ng/g</td>
<td>Absolute expanded uncertainty in ng/g</td>
</tr>
<tr>
<td>fresh water</td>
<td>lead</td>
<td>0.006 to 300</td>
<td>0.0003 to 30</td>
</tr>
</tbody>
</table>

Mechanism(s) for measurement service delivery: CRM SLRS-5
Uncertainty convention 2.
Approved on 27 March 2013
Internal NMI service identifier: NRC/TEW11

### France, LNE (Laboratoire national de métrologie et d'essais)

<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th>Relative expanded uncertainty in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>fresh water</td>
<td>lead</td>
<td>1 to 100</td>
<td>5 to 2</td>
</tr>
</tbody>
</table>

Mechanism(s) for measurement service delivery: Calibration
Approved on 27 March 2013
Uncertainty convention 1
Internal NMI service identifier: LNE/CMI-37-101-3

### Germany, PTB (Physikalisch-Technische Bundesanstalt)

<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th>Relative expanded uncertainty in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>natural water</td>
<td>lead</td>
<td>50 to 80</td>
<td>3</td>
</tr>
</tbody>
</table>

Mechanism(s) for measurement service delivery: Reference measurement
Uncertainty convention 1.
Approved on 27 March 2013
Internal NMI service identifier: PTB/AC-Was-002

Just examples, not a complete list

- CRM
- Will value-assign customer-provided material
- Will value-assign customer-provided material
<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th>Range of certified values in reference materials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mass fraction in µg/kg</td>
<td>Relative expanded uncertainty in %</td>
</tr>
<tr>
<td>river water and drinking water</td>
<td>lead</td>
<td>0.001 to 10</td>
<td>15 to 1</td>
</tr>
</tbody>
</table>

**Mechanism(s) for measurement service delivery:** NMIJ CRM 7202
Uncertainty convention 2.
Approved on 12 March 2013
Internal NMI service identifier: NMIJ/5-01-10

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**Water, Fresh water**

**Mexico, CENAM (Centro Nacional de Metrologia)**

Complete CMCs in Chemistry for Water for Mexico (.pdf file)

<table>
<thead>
<tr>
<th>Matrix or material</th>
<th>Analyte or component</th>
<th>Dissemination range of measurement capability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>fresh water</td>
<td>lead</td>
<td>5 to 30</td>
<td>1 to 3</td>
</tr>
</tbody>
</table>

**Mechanism(s) for measurement service delivery:** Value-assignment through MRTC program
Approved on 27 March 2013.
Uncertainty convention 1
Internal NMI service identifier: CENAM/620-Q008-007
A Context for the Complexity of Chemical and Biological Measurements

- According to a study released by the Council for Chemical Research, *chemistry is core or important to virtually all industrial sectors and technology areas* – *“Measuring Up: Chemical R&D Counts for Everyone”, CCR, 2006*

- Chemical measurements are multidimensional
  - a large number of chemical entities (>10^5)
  - in a broad range of matrices (10^?)
  - and mass fractions ranging from <10^{-12} to 1

- For *metrology in chemistry* the task is to determine the quantity of a specific chemical entity and not merely "amount of substance"

**Whereas for Physical Measurement:** What’s the mass of Jim? 90 kg

**Chemical:** How much cholesterol is there in Jim’s blood? 50 mg/dL

Understanding life processes requires even more

**Biological:** Which cholesterol-lowering drug would be best for Jim in terms of both efficacy and potential side effects? 
Trial and Error → Precision Measurement: taking into account an individual's personal DNA
... an example of this complexity
Regulated Classes of Chemicals in Foods

<table>
<thead>
<tr>
<th>Nominal Concentrations of Measurands in Foods</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 g/g</td>
</tr>
<tr>
<td>1 mg/g</td>
</tr>
<tr>
<td>1 μg/g</td>
</tr>
<tr>
<td>1 ng/g</td>
</tr>
<tr>
<td>1 pg/g</td>
</tr>
</tbody>
</table>

- 50 to 60 elemental species of importance
- >10^5 organic species in a wide variety of sample types
- covering 12 orders of magnitude in concentration.

All of these measurements are impacted by legislation.
First, a few definitions:

**International Vocabulary of Measurement**


**Reference Material (RM):**

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

(with notes and examples in full document)

…NOTE 8 ISO/REMCO has an analogous definition [45] but uses the term “measurement process” to mean ‘examination’ (ISO 15189:2007, 3.4), which covers both measurement of a quantity and examination of a nominal property.


**Reference Material (RM)**

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 1:* RM is a generic term.

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

*Note 3.* Uses may include the calibration of a measurement system, assessment of a measurement procedure, assigning values to other materials, and quality control.

*Note 4.* A single RM cannot be used for both calibration and validation of results in the same measurement procedure.

*Note 5:* VIM has an analogous definition (JCGM 200:2008 5.13), but restricts the term “measurement” to apply to quantitative values and not to qualitative properties. However Note 3 of VIM 5.13 specifically includes the concept of qualitative attributes, called “nominal properties”.

(For quality systems and SRM purposes, NIST uses the ISO Definition.)
certified reference material

CRM

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.


EXAMPLE Human serum with assigned quantity value for the concentration of cholesterol and associated measurement uncertainty stated in an accompanying certificate, used as a calibrator or measurement trueness control material.

NOTE 1 ‘Documentation’ is given in the form of a ‘certificate’ (see ISO Guide 31:2000).

NOTE 2 Procedures for the production and certification of certified reference materials are given, e.g. in ISO Guide 34 and ISO Guide 35.

NOTE 3 In this definition, “uncertainty” covers both ‘measurement uncertainty’ and ‘uncertainty associated with the value of a nominal property’, such as for identity and sequence. “Traceability” covers both ‘metrological traceability of a quantity value’ and ‘traceability of a nominal property value’.

NOTE 4 Specified quantity values of certified reference materials require metrological traceability with associated measurement uncertainty (Accred. Qual. Assur.:2006) [45].

NOTE 5 ISO/REMCO has an analogous definition (Accred. Qual. Assur.:2006) [45] but uses the modifiers “metrological” and “metrologically” to refer to both quantity and nominal property.
## ISO REMCO Standards - Published and Revisions under development

[www.iso.org/iso/home/store/catalogue_tc](www.iso.org/iso/home/store/catalogue_tc)

### Standards and projects under the direct responsibility of ISO/REMCO Secretariat

<table>
<thead>
<tr>
<th>Standard and/or project</th>
<th>Link</th>
</tr>
</thead>
</table>
Metrological Traceability: 2.41 (6.10)
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
(VIM (3rd edition, 2008))

2.26 (3.9) measurement uncertainty
uncertainty of measurement
uncertainty
non-negative parameter characterizing the dispersion of the quantity values being attributed to a measurand, based on the information used.
(VIM (3rd edition, 2008))

Metrological traceability and global comparability are the basis for mutual recognition ... and international trade ... and confidence in data used in making decisions relating to health, safety, commerce, and/or scientific excellence.
Certified Reference Materials (CRMs) and Proficiency test (PT) materials with property values that are:

- appropriate for their intended use, and
- recognized as appropriate by users of these material and users of data resulting from their use

are a critical component of schemes for providing mutual recognition and confidence in chemical measurements worldwide.
• However, there are many different providers / sources of Reference Materials (RMs) and Certified Reference Materials (CRMs).

• Typically, these meet the accepted definitions of an RM or CRM. Providers include:
  – National Measurement Institute (NMI) or designated institute (DI) responsible for national standards
  – Reference Laboratory as designated by a governmental body, regulatory body, customer sector group, national or international organization, provided for by normative standard requirements, etc. – may provide CRMs
  – Commercial providers of certified reference materials, reference materials and/or proficiency testing

• There are appropriate roles and needs for these various CRMs/RMs in the metrological hierarchy.

• However, the use of the term “Certified Reference Material” is not restricted and thus can be misused.
Within this international framework

The typical role of an NMI (and/or Officially Designated Institutes in a Distributed System) is to establish and maintain:

Scientifically-Sound, Metrologically-Based Competencies and Measurement Capabilities that are internationally Vetted and Recognized

To provide calibration and measurement services disseminated to Customers via mechanisms such as:

– Validated Reference Methods
– Certified Reference Materials
– Value-assignment of customer-provided samples or materials (including PT samples)
– Reference Data
– Measurement Services for other Government Agencies
– Etc.
From Section 9 of the ISO Guide 35 (2006) for Reference Materials - but also applies to PT materials –

“There are a number of technically valid approaches to the assignment of property values.

These include measurement with one or more methods involving one or more laboratories.

An appropriate approach can be chosen depending on the type of reference material, its end-use requirements, the qualifications of the laboratories involved, the quality of the method or methods, and the ability to estimate the uncertainty associated with the characteristics realistically”.
A number of approaches are used to certify values (with appropriate uncertainty) in CRMs and for value-assignments of PT Materials. These include:

a) Use of **Known / Calculated values** - with results determined by specific test item formulation (e.g. manufacture or dilution).

b) Use of **Validated Reference Procedure(s)**

c) Use of a **specified Measurement Process** (method dependent, empirical method).

d) **Consensus values from expert laboratories** - expert laboratories should have demonstrated competence . . .

e) **Consensus values from participant laboratories**

f) **Combinations of these**

Different approaches to be used will require different reference material provider competencies.
Why SI Traceability?

*Traceability to the SI leads to measurement results that have three properties.*

**Stable**
- Results from measurements of the same quantity against the same reference in one laboratory will be stable over time.

**Comparable**
- Results from measurements of the same quantity against the same reference in different laboratories will be comparable over both time and space.

**Coherent**
- Results from measurements of the same quantity against different references will be same over both time and space.

- Traceability to the SI provides all three of these.

- Other approaches to standardization only provide the first two.
Planning / Design / Implementation of value-assignment project to address fit-for-purpose need includes appropriate:

- choice of “measurand”
- choice and appropriate implementation of value assignment mechanism/approach
  - commutability
- traceability linkage
- homogeneity and stability assessment
- certificate/report
- uncertainty components and expression

If you are choosing a CRM or PT to use for your program, you also should evaluate these in terms of fit for purpose for your uses.
Typical Stakeholders include:

- National Metrology Institute (NMI)
- CRM Provider
- CRM Provider Accreditor
- PT Provider Accreditor
- PT Provider
- Testing Laboratories
- Users of Testing Laboratory data, e.g., its customers’ regulators and trading partners, decision-makers using chemical measurement data, etc.
- Users of Testing Laboratory PT performance results, e.g., accrediting/certifying authority, regulatory program, etc.

Communication amongst these is critical
For measurand:
What is the assigned-value meant to provide, at what uncertainty is needed:

- “Truth”
  - Realization of the SI units: Mole, kilogram, meter,
- What a standard method should get
  - Method-dependent value
  - Realization of operationally defined process
- Other???
  - “Lead” in a soil material as xx mg/kg (estimate of “truth”)  
  - or “Lead by US EPA Method yyy” as zz mg/kg in a soil material  
  - or ???

- What degree of uncertainty is required for the assigned-value for the material to be fit-for-purpose?
Hypothetical: Superimposing of US acceptability limits

IMEP-9: Trace elements in Water
Certified range ($\pm U = 2u_c$): 81.0 - 85.4 nmol·L$^{-1}$

Results from all participants.
• “Rule of three” or “Rule of four” - the expanded uncertainty of the CRM or PT is one-third or one-fourth of that uncertainty needed for a given calibration, validation, or needed to assess PT performance.

• often cited for CRMs, PTs, etc. as criteria for its uncertainty being sufficiently small relative to its intended use; usually possible with available, advanced techniques but sometimes not.
Experimental Planning:

- The issuance of a NIST CRM/RM is guided by an experimental plan that incorporates an assessment of the measurement need, material type and physical form, the required measurement results, and statistical criteria for sampling and analysis. Key components:
  - Required properties of the base material and SRM/RM unit
  - Statistical plan for subsampling and measurement
  - Required scope of measurement data and limits of uncertainty
  - Techniques and methods to be used in the measurement process
  - Measures of traceability and verification
  - Provision for maintaining the SRM/RM (stability tests) and propagation of the SRM/RM
In chemical measurements: Two main Types of Certified Reference Materials:

- Primary calibrators (e.g., calibration solution with known values and associated uncertainty)

- Method validation materials (Accuracy Controls) (e.g., with certified values and associated uncertainty for specific components in a matrix.)
Chemical Measurements

- Chemical measurements involve the determination of the quantity of a specific chemical entity and not merely "amount of substance" (i.e., requires confirmation of identify as well as amount)
  - A primary reference for the chemical to be measured (a reference material of known chemical purity) is required to provide the basis for establishing the relationship between instrumental response and the amount of this chemical present in the sample.
  - Identify of chemical entity used as calibrant and of what measuring must be confirmed.

Example of calibration curve

![Calibration Curve](image)

- Mass/g of "Unknown" Inst Response
- Mass/g, calibrant
- $y = 0.77346x + 0.00097$
- $R^2 = 0.99999$
In value-assigning a calibrator CRM or a formulated CRM or PT material from known components – critical point isvassessment of purity of components if a higher level CRM is not available.

**Assessment of Purity of Organic Species: Challenges**

**Typically:**
- Until recently, no direct assay method, now q1H-NMR can be used in a number of cases
- small amount of precious material available for purity assessment
- rely upon determination of impurities where:
  - Purity = 100% - Sum of determined impurities
- impurities are detected and measured by a variety of tests
- reference materials of impurities often not available which may preclude identification and calibration in measurement of impurities
- the tests used for determination of impurities are not all measuring the same measurand(s).
  - approaches typically used for combining results from different measurement approaches (but for the same expected measurand) and for the subsequent combining of uncertainty components often are not appropriate
  - Interpretation of results requires sound professional judgment based on a good understanding of the chemistry involved. **Statistics AND scientific judgment are used in estimating purity and uncertainty**
  - No “one size fits all” as of yet
Mass Balance Approach - organics:

\[ \text{Purity} = (100 - I_T) \% \]

Uncertainty – include components for potential impurities:

- Not detected with techniques used
- Below limit of detection with techniques used
- Not resolved with techniques used

*Technique* = as determined by specified measurement technique(s)

- Residue (Non-volatile impurities)
- Inorganics
- Water (as relevant)
- Impurities: Properties more similar to those of primary component
Proposes a general approach to the assessment of purity is proposed that includes:

- the determination of what is required for a material to be fit for its intended use
- the determination of purity by direct or indirect means with a discussion of appropriate analytical techniques
- the combining of various analytical results, and the proper presentation of available information.

The certificates for a number of materials are evaluated against this approach as case studies.

Available free from NIST
NIST SP 1012 was vetted internationally with input from members of CCQM Organic Analytical Working Group and provides:

- guidelines for the evaluation of the purity of organic chemicals, usually high-purity chemicals, intended for use as reference materials or primary standards and for the certification of these materials such that assigned values can be considered as metrologically sound and traceable to base units of mass and amount of substance.

- descriptions of existing methodology for the analysis and certification of high-purity reference materials
  - metrological concepts and nomenclature
  - procedures used for preparation and certification of high-purity reference materials including analytical methods
  - appropriate combining of different measurements. The consequences of decisions on required purity, the nature of allowed impurities, traceability to other standards, quantitative characterization, measurement uncertainties, and what information needs to be included in a certificate are considered.
A new IUPAC Project was initiated and is expanding and updating this.

IUPAC Project 2013-025-2-500

Methods for the SI Value Assignment of the Purity of Organic Compounds for use as Primary Reference Materials and Calibrators
CONTENTS

Preface—L. A. K. Staveley (UK)

Introduction—L. A. K. Staveley (UK)

The concept of purity, and its bearing on methods used to characterize purity—W. M. Smit (Netherlands)

Thermal methods—E. F. G. Herington (UK)

Density measurements—Tomasz Plebanski (Poland)

Vapour pressure and boiling temperature measurements—Aleksander Kreglewski (USA)

Refractive index—Charles Proffer Saylor (USA)

Chromatography—D. Ambrose (UK)

Mass spectrometry—L. B. Westover and J. C. Tou (USA)

Optical spectroscopy—W. G. Potts and Warren Crummett (USA)

Nuclear magnetic resonance spectroscopy—Jerry P. Heeschen (USA)

Raman spectroscopy—D. A. Long (UK)

The use and availability of standard samples—Daniel R. Stull (USA)
NIST Modes of Certification of Reference Materials for Chemical Measurements -- **HISTORICAL**

- method(s) of high precision
  - for which sources of bias have been rigorously investigated
  - applicability of the method(s) have been demonstrated and documented across a range of diverse matrices
- by two or more independent and reliable methods
  - whose estimated uncertainties are small, relative to the accuracy required for certification or SRM purpose and use
- measurement via a network of qualified laboratories

- Various terms such as certified value, information value, reference value, non-certified value, etc. were used on NIST SRM Certificates ... with no clear explanation of their meaning for our customers, for MRA and peers, and for us!
- These terms are also used on products from commercial CRM providers – with many different meanings.
To define terms and criteria for NIST CRMs for chemical measurements - as a CRM Provider, NIST has provided SP 260-136 to the public:

- describes seven modes currently used at NIST for value-assigning SRMs and RMs for chemical measurements
- defines data quality descriptors used at NIST for these SRMs and RMs
  - NIST Certified Value
  - NIST Reference Value
  - NIST Information Value
- links these modes to these three data quality descriptors

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**NIST Special Publication 260-136**

*Standard Reference Materials*  
*Definitions of Terms and Modes Used at NIST for Value-Assignment of Reference Materials for Chemical Measurements*

Analytical Chemistry Division  
Chemical Science and Technology Laboratory

T. Gills, J. Colbert, R. Gettings, and B. MacDonald  
Standard Reference Materials Program  
Technology Services  
National Institute of Standards and Technology  
Gaithersburg, MD 20899-8390

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**View/download from:**  
NIST Certified Value
(for Chemical Composition and Related Properties)

Provided on a NIST SRM Certificate -

• as a value for which NIST has the highest confidence in its accuracy in that all known or suspected sources of bias have been fully investigated or accounted for
  – requires NIST measurements and oversight of the experimental design for the value-assignment process

• with an associated uncertainty that
  – generally specifies a range within which the true value is expected to lie at a level of confidence of approximately 95% if the sample is homogeneous
  – generally represents a prediction interval within which the true values of 95% of all samples are expected to lie at a stated level of confidence if significant sample heterogeneity is included
Terms and definitions for use with NIST Reference Materials

NIST Reference Value
(for Chemical Composition and Related Properties)

Provided on a NIST Certificate/Certificate of Analysis/Report of Investigation -

• as a best estimate of the true value where all known or suspected sources of bias have not been fully investigated by NIST

• with an associated uncertainty that may not include all sources of uncertainty and may represent only a measure of the precision of the measurement method(s)
Modes Used at NIST for Value-Assignment of Reference Materials for Chemical Measurements

1. Certification at NIST Using a Primary Method with Confirmation by Other Method(s)

2. Certification at NIST Using Two Independent Critically-Evaluated Methods

3. Certification/Value-Assignment Using One Method at NIST and Different Methods by Outside Collaborating Laboratories

4. Value-Assignment Based On Measurements by Two or More Laboratories Using Different Methods in Collaboration with NIST

5. Value-Assignment Based on a Method-Specific Protocol

6. Value-Assignment Based on NIST Measurements Using a Single Method or Measurements by an Outside Collaborating Laboratory Using a Single Method

7. Value-Assignment Based on Selected Data from Interlaboratory Studies
Note: This NIST document does NOT necessarily apply to YOUR use of various terms regarding value-assignment of CRMs and PTs:

• There are many different sources / requirements for CRMs and PTs
  – National Measurement Institute (NMI) or designated institute (DI) responsible for national standards
  – Reference Laboratory – CRMs and/or PTs for a specific sector, governmental body, regulatory agency, or ……etc.
  – Commercial providers of certified reference materials, reference materials and/or proficiency testing

• There are appropriate roles and needs for all of these materials and providers.

However, you should ask what is meant by terms and titles used by providers of CRMs you use if it is not clear in accompanying documentation.
Modes used at NIST for Value Assignment of Reference Materials for Chemical Measurements:

**Mode 1:** Certification at NIST Using a Primary Method with Confirmation by Other Method(s)

- All potentially significant sources of error have been evaluated explicitly for the application of the method and the matrix under investigation.
- Confirmation can be accomplished by:
  - determination of certified constituents in other SRM(s) or CRM(s) of similar matrix/concentration range;
  - a second NIST technique with appropriate controls; or,
  - results of measurements from selected outside collaborating laboratories with appropriate experience.
- The required level of agreement between the primary method and any confirmatory method(s) must be predetermined and specified in the experimental plan.
Primary Method: Actually – has POTENTIAL for being a primary technique

Example: Isotope Dilution Mass Spectrometry (IDMS) is often referred to as a “primary method”:

There Are Potential Pitfalls That One Must Be Aware of when implementing – are critical parts of method validation:

• Isotope Effects
• Non-equilibration
• Chemical Interferences
• Cross Contributions
• Calibration Errors
• Instrument Instability
• Memory Effects
• Differences In Fragmentation
Mode 2: Certification at NIST Using Two Independent Critically-Evaluated Methods

- Methods are selected to minimize common steps in sample preparation and the final analytical measurement techniques.
- Methods have no known significant sources of error in common.
- Methods/procedures selected are appropriate for the required precision and accuracy for measurement of the analyte(s) of interest in this matrix.
- Level of between-method agreement required for certification is pre-determined and documented in experimental plan.
Rationale – natural matrix samples:

Using Validated Procedures

*that*

exploit differences in separation and selectivity characteristics

Extraction/Digestion  Isolation  Measurement

minimizes possibility of undetected bias in resulting certified concentrations
PCBs and Pesticides: SRM 1946

Method 1
- pressurized fluid extraction
- duplicates of 10 samples (1 g) CH₂Cl₂
- size exclusion chromatography (NH₃)
- liquid chromatography (NH₃)
- PCBs, less polar pesticides
- GC-ECD I
  - 20 samples
  - 5% phenyl methyl polysiloxane column

Method 2, 3
- pressurized fluid extraction
- 6 samples (1 g) CH₂Cl₂
- size exclusion chromatography (NH₃)
- liquid chromatography (NH₃)
- PCBs, less polar pesticides
- more polar pesticides
- GC-ECD II A
  - 6 samples
  - 5% phenyl methyl polysiloxane column

Method 4
- Soxhlet extraction
- 6 samples (3 g) hexane:acetone (1:1, v/v)
- sulfuric acid
- solid phase extraction (silica)
- GC/MS I
  - non-polar proprietary column
  - EI

Method 5
- Soxhlet extraction
- 6 samples (3 g) hexane:acetone (1:1, v/v)
- sulfuric acid
- solid phase extraction (silica)
- GC/MS II
  - 5 % phenyl methyl polysiloxane column
  - NICI

Method 6
- Soxhlet extraction
- 3 samples (1.5 g) CH₂Cl₂
- size exclusion chromatography
- solid phase extraction (silica)
- GC/MS III
  - non-polar proprietary column
  - EI

Method 7
- interlaboratory comparison (1999)
- 30 sets of results

NIST SRM 1946: Lake Superior Fish Tissue (fresh, frozen)
Combining results from two or more analytical methods to obtain assigned value and associated uncertainty

• Again:
  – Not one-size-fits-all are numerous technically valid approaches and issue is still under much discussion
  – Not just a statistical activity – joint of chemists with statisticians
  – A number of valid approaches have been used

Modern use of Monte-Carlo techniques
**Mode 3:** Certification/Value-Assignment Using One Method at NIST and Different Methods by Outside Collaborating Laboratories

- NIST method and the outside collaborating laboratory methods must have demonstrated accuracy in the matrix under investigation.
- Method used by outside collaborating laboratory should be different from the NIST method as required by the “Two Independent NIST Methods” mode.
- Data reporting requirements for outside collaborating laboratories are specified in the experimental plan and their reports should contain sufficient information to evaluate all significant sources of uncertainty.
Mode 4: Value-Assignment Based on Measurements by Two or More Laboratories Using Different Methods in Collaboration with NIST

- The outside collaborating laboratory methods must have demonstrated accuracy in the matrix under investigation.
- Methods used by the outside collaborating laboratories should be different as required by the “Two Independent NIST Methods” mode.
- Data reporting requirements for the outside collaborating laboratories are specified in the experimental plan and their report should contain sufficient information to evaluate all significant sources of uncertainty, unless a large number of labs/methods submit data, in which case the “Interlaboratory Study” criteria apply.
Mode 5: Value-Assignment Based on a Method-Specific Protocol

- Protocol used should be one that is recognized by the user community as the prescribed method for measurement of the analyte (or property) of interest in this matrix.
- Only data from experienced practitioners of the method should be used.
- Measurements using the method-specific protocol can be made by NIST, outside laboratories, or both.
- Method dependent value-assignment will typically involve no less than three experienced practitioners of the method.
5. Step 1. Specification of the Measurand

5.1. In the context of uncertainty estimation, “specification of the measurand” requires both a clear and unambiguous statement of what is being measured, and a quantitative expression relating the value of the measurand to the parameters on which it depends. These parameters may be other measurands, quantities which are not directly measured, or constants. It should also be clear whether a sampling step is included within the procedure or not. If it is, estimation of uncertainties associated with the sampling procedure need to be considered. All of this information should be in the Standard Operating Procedure (SOP).

5.2. In analytical measurement, it is particularly important to distinguish between measurements intended to produce results which are independent of the method used, and those which are not so intended. The latter are often referred to as empirical methods. The following examples may clarify the point further.

EXAMPLES:

1. Methods for the determination of the amount of nickel present in an alloy are normally expected to yield the same result, in the same units, usually expressed as a mass or mole fraction. In principle, any systematic effect due to method bias or matrix effect would need to be corrected for, though it is more usual to ensure that any such effect is small. Results would not normally need to quote the particular method used, except for information. The method is not empirical.

2. Determinations of “extractable fat” may differ substantially, depending on the extraction conditions specified. Since “extractable fat” is entirely dependent on choice of conditions, the method used is empirical. It is not meaningful to consider correction for bias intrinsic to the method, since the measurand is defined by the method used. Results are generally reported with reference to the method, uncorrected for any bias intrinsic to the method. The method is considered empirical.

3. In circumstances where variations in the substrate, or matrix, have large and unpredictable effects, a procedure is often developed with the sole aim of achieving comparability between laboratories measuring the same material. The procedure may then be adopted as a local, national or international standard method on which trading or other decisions are taken, with no intent to obtain an absolute measure of the true amount of analyte present. Corrections for method bias or matrix effect are ignored by convention (whether or not they have been minimised in method development). Results are normally reported uncorrected for matrix or method bias. The method is considered to be empirical.

5.3. The distinction between empirical and non-empirical (sometimes called rational) methods is important because it affects the estimation of uncertainty. In examples 2 and 3 above, because of the conventions employed, uncertainties associated with some quite large effects are not relevant in normal use. Due consideration should accordingly be given to whether the results are expected to be dependent upon, or independent of, the method in use and only those effects relevant to the result as reported should be included in the uncertainty estimate.
ISO/TS 21748 Guidance for the use of repeatability, reproducibility and trueness estimates in measurement uncertainty estimation; 2004 (See Examples In Annex C of Guide)

Taken from Introduction:
• Laboratories operating under ISO 17025 accreditation and related systems are accordingly required to evaluate measurement uncertainty for measurement and test results and report the uncertainty where relevant.
• The GUM is a widely adopted standard approach. However, it applies to situations where a model of the measurement process is available.
• A wide range of standard test methods is, however, subjected to collaborate study in accordance with ISO 5725-2.
• ISO 21748 provides an appropriate and economic methodology for estimating uncertainty associated with the results of these methods, which complies fully with the relevant principles of the GUM.

From 5.2 of ISO/TS 21748:
“..effects not observed within the context of the collaborative study must be demonstrated as negligible or explicitly allowed for.”

From 6.2 of ISO/TS 21748:
“where the precision differs in practice from that expected from the studies..,the associated contributions to uncertainty should be adjusted…”
Heterogeneity, Stability, Other Components of Uncertainty of Assigned Value

For CRMs and PTs –

• Important to includes component for any significant heterogeneity in the material in the uncertainty of the assigned value.

• If there is a predictable change in the assigned value over the time of use of the material, the uncertainty is expanded to include this component.

• Sometimes, the uncertainty of an assigned value is expanded to allow for use of the assigned value over a wider range of temperatures. E.g., If the assigned value of a formulated solution was prepared and value-assigned on a mass/mass basis – the value may to converted to mass/volume basis as well. The uncertainty would then be expanded to account for uncertainty in determination of density of the solution and to account for change in assigned value, say from 20 to 25 degrees C.
Why use a “confirmatory method” for case where value-assignment of a property of a material is being made using data from the gravimetric preparation (formulation)?

In this case, where property value needed for this material is “best estimate of truth” (i.e., not a method-dependent value)):

Typically, formulation data results in a value-assignment of the property value of interest in the “bulk” sample.

- Cannot always correctly assume that the property value(s) of interest of the material as packaged for the user is the same of that of the bulk material

Typically, these analyses would be required anyway for the appropriate assessment of degree of homogeneity of the material as being provided to user – bottled/ampouled/etc. – packaged.
Example*: Lindane in dichloromethane

• Bulk material:

Value for Lindane from gravimetric preparation = 34.4 ug/g

(34.6 mg of Lot xyz of Lindane) * (0.994 g “Lindane” per g of “Lot xyz of Lindane”)

1000 g of total solution (lindane plus dichloromethane)

• Ampouled material:

Mean Value for Lindane from GC-ECD analyses of ampouled material
(validated method with appropriately value-assigned calibrants) = 36.1 ug/g

Further analysis of GC data:

*of course, this – and other examples used - should include/show evaluation/ expression of uncertainty; however, for simplicity, it is not included/shown here
Examples of Relevant Standards
CRMs

ISO/IEC 17025: 2005 “General requirements for the competence of testing and calibration laboratories” (being systematically reviewed in 2015)


http://www.ilac.org/ click on "Publications" and also "Library" for additional resources.

Committee for International Traceability in Analytical Chemistry
http://www.citac.cc

www.bipm.org Link to Key Comparison Database and then to BIPM KCDB – Appendix C CMCs

Numerous standards-related documents have been translated to Portuguese: See Vera Poncano for current listing.
Responsibilities:

**CRM Material Providers:**
- Provide design/process to assure “quality” of reference or proficiency test material and its assigned value(s)
- Provide documentation and information to user to support value-assignment and claim of traceability
- Provide information as to intended use and appropriate use of material
- Appropriate use of ISO Guide 30 series and other relevant guides and standards

**Users of material and/or users of resulting analytical data:**
- Assess relevancy and suitability of CRM, including the specified measurand, the measurand assigned value, metrological traceability, and its associated uncertainty, for THEIR intended use and program / regulatory / quality system needs
- Appropriate use of CRM and RM to maintain validity and to support user’s metrological traceability claim.
A Global Challenge

- Are seeing exponential increase in requests for CRMs and Proficiency Tests – especially in organic and bioscience areas

- With the immense number of analyte-matrix-concentration levels, etc., how can we cover our “measurement space” effectively and efficiency?
  - Certified Reference Materials
  - Proficiency Test Samples with SI-traceable Reference Values
  - Neat Calibration materials with assigned purity

- Not achievable to have one-to-one match for each combination. So:
  How do laboratories realize metrological traceability?
  What do various assessors expect/require?

With no quantum methods typically available,

- Need an efficient strategy for CRM producers to collectively establish a “virtual system” to provide and maintain a set of CRMs that meet global needs and cover the chemical measurement “space” to meet metrological requirements; with a range of CRMs of “higher order” .. to CRMs needed for testing laboratories for more routine use.
Metrology Program with CRMs and PTs that are fit for purpose and appropriately value-assigned pays Significant Dividends to a Nation’s Economy and Quality of Life

- Impacts innovation, commerce, and economic & social sustainability
- Is a critical part of our global infrastructure
NIST Website:  www.nist.gov/

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Muito Obrigada!

Thank you!

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