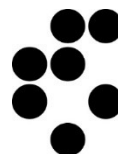




science and policy
for a healthy future

Use of (certified) reference materials in HBM

Milena Horvat, Janja Snoj Tratnik,
Darja Mazej



Institut "Jožef Stefan", Ljubljana, Slovenija

2st HBM4EU Training School 2018
Nijmegen, 19.11.2018

International Vocabulary of Metrology – Basic and General Concepts and Associated Terms

VIM, 3rd edition, JCGM 200:2008

<http://www.bipm.org/en/publications/guides/vim.html>

Eurachem guides

<https://www.eurachem.org/index.php/publications/guides>

ISO/IEC Guide 99:2007, *International vocabulary of metrology – Basic and general concepts and associated terms (VIM)*



Metrology

METROLOGY = Science of Measurement

Understanding

the measurement procedure

Meter convention

- Diplomatic treaty
- Paris, May 20, 1875
- SI metric system
- Seven base units
 - Common system of units
 - International uniformity in measurement
 - Harmonized legislation

Metric System (SI)

- | | |
|-----------------------|------------------------|
| • Mass | kilogram (kg) |
| • Length | meter (m) |
| • Time | second (s) |
| • Temperature | kelvin (K) |
| • Electric current | ampere (A) |
| • Amount of substance | mole (mol) |
| • Luminous Intensity | candela (cd) |

Metric System (SI)

- All other units are derived from primary seven
 - **Density:** kilogram per cubic metre kg/m^3
 - **Speed:** metre per second (m/s)
 - **Concentration:** mol per cubic metre (mol/m^3)
gram per kilogram (g/kg)
 - **Volume:** $1000 \text{ L} = 1 \text{ m}^3$
 - **Surface, pressure, viscosity, etc.**
- **Ionising radiation & radioactivity:**
 - 1 Bq = decay per second



Redefinition of the kilogram

NEWS IN FOCUS

IN FOCUS NEWS

METROLOGY

Experiments to redefine kilogram converge at last

After a fraught few years, results agree in time to meet a 2018 deadline.

BY ELIZABETH GIBNEY

For decades, metrologists have strived to retire 'Le Grand K' — the platinum and iridium cylinder that for 126 years has defined the kilogram from a high-security vault outside Paris. Now it looks as if they at last have the data needed to replace the cylinder with a definition based on mathematical constants.

The breakthrough comes in time for the kilogram to be included in a broader redefinition of units — including the ampere, mole and kelvin — scheduled for 2018. And this week, the International Committee for Weights and Measures (CIPM) will meet in Paris to thrash out the next steps.

"It is an exciting time," says David Newell, a physicist at the US National Institute of Standards and Technology (NIST) in Gaithersburg, Maryland. "It is the culmination of intense, prolonged efforts worldwide."

The kilogram is the only SI unit still based on a physical object. Although experiments that could define it in terms of fundamental constants were described in the 1970s, only in the past year have teams using two completely different methods achieved results that are both precise enough, and in sufficient agreement, to topple the physical definition.

Redefinition will not make the kilogram more precise, but it will make it more stable. A physical object can lose or gain atoms over time, or be destroyed, but constants remain the same. And a definition based on constants would, at least in theory, allow the exact kilogram measure to be available to someone anywhere on the planet, rather than just those



A replica of the kilogram mass reference, which is set to be replaced by a definition based on constants.

of them use different methods.

One method, pioneered by an international team known as the Avogadro Project, involves counting the atoms in two silicon-28 spheres that each weigh the same as the reference kilogram. This allows them to calculate a value for Avogadro's constant, which the researchers convert into a value for Planck's constant.

"I think every metrologist worried, 'What if they never

Another method uses a device called a watt balance to produce a value for Planck's constant by weighing

Project, and chair of the CIPM's Consultative Committee for Units. The first sign of progress came after the Measurement Science and Standards laboratory in Ottawa, part of Canada's National Research Council (NRC), bought and rebuilt a watt balance originally constructed at the UK National Physical Laboratory in Teddington.

In a new lab, a fresh NRC team factored in some predicted but as yet unaccounted for systematic errors, and the result, published¹ in January 2012, inched closer to the Avogadro Project's silicon-sphere result.

ANDREW BRISQ/ISTOCK/PHOTODISC

**How to ensure appropriate measurements and
monitor changes in time and space?**

Analytical measurements
need to be **comparable**
in time and space ...

traceability is the best/only way to achieve this goal.



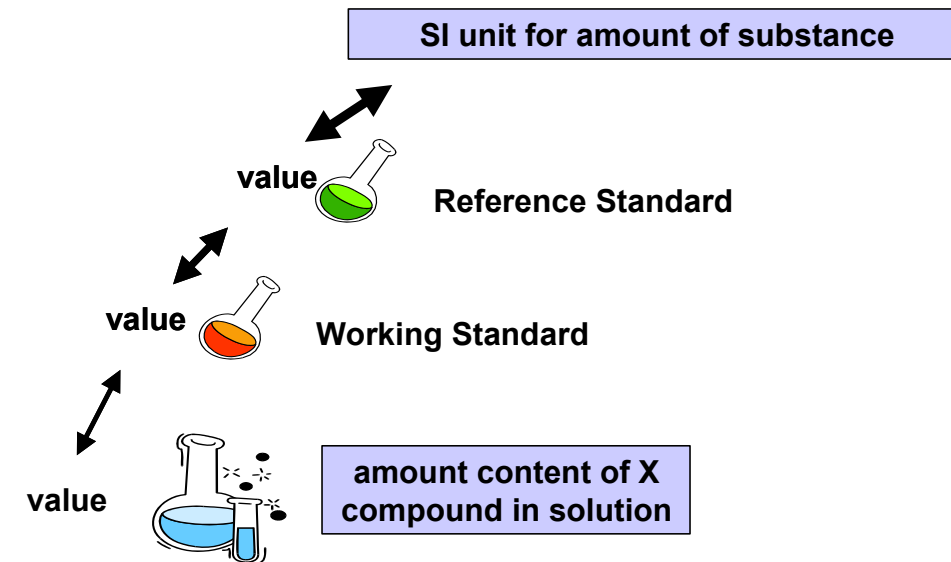
Any measurement is the establishment
of a **RATIO** of an **unknown** to a **known**
quantity

Defining the agreed unit
Expressed in the same unit

VIM definition

“ ... the **property** of the result of a measurement or the value of a standard whereby it can be related **to stated references**, usually national or international standards, through an **unbroken chain of comparisons** all having stated uncertainties.”

Traceability of Chemical Measurements



Sampling + Processing + Measurement = Result

**Representative
Appropriate
Contamination
Stability
Handling**

**Dissolution
Extraction
Dilution**

**Comparison to SI units
or conventional scale**

\pm uncertainty

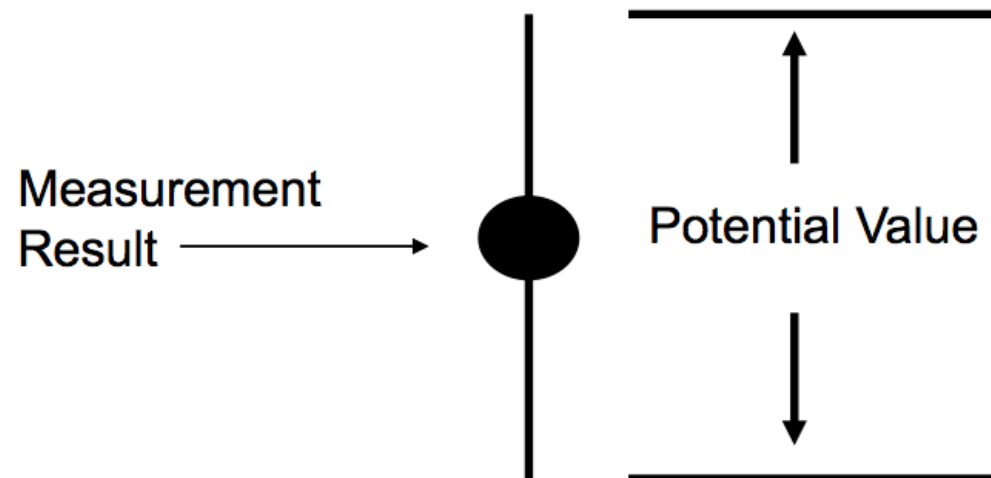
(VIM)

„a **parameter associated with the result** of a measurement, that characterises the **dispersion of the values** that could reasonably be attributed to the measurand“

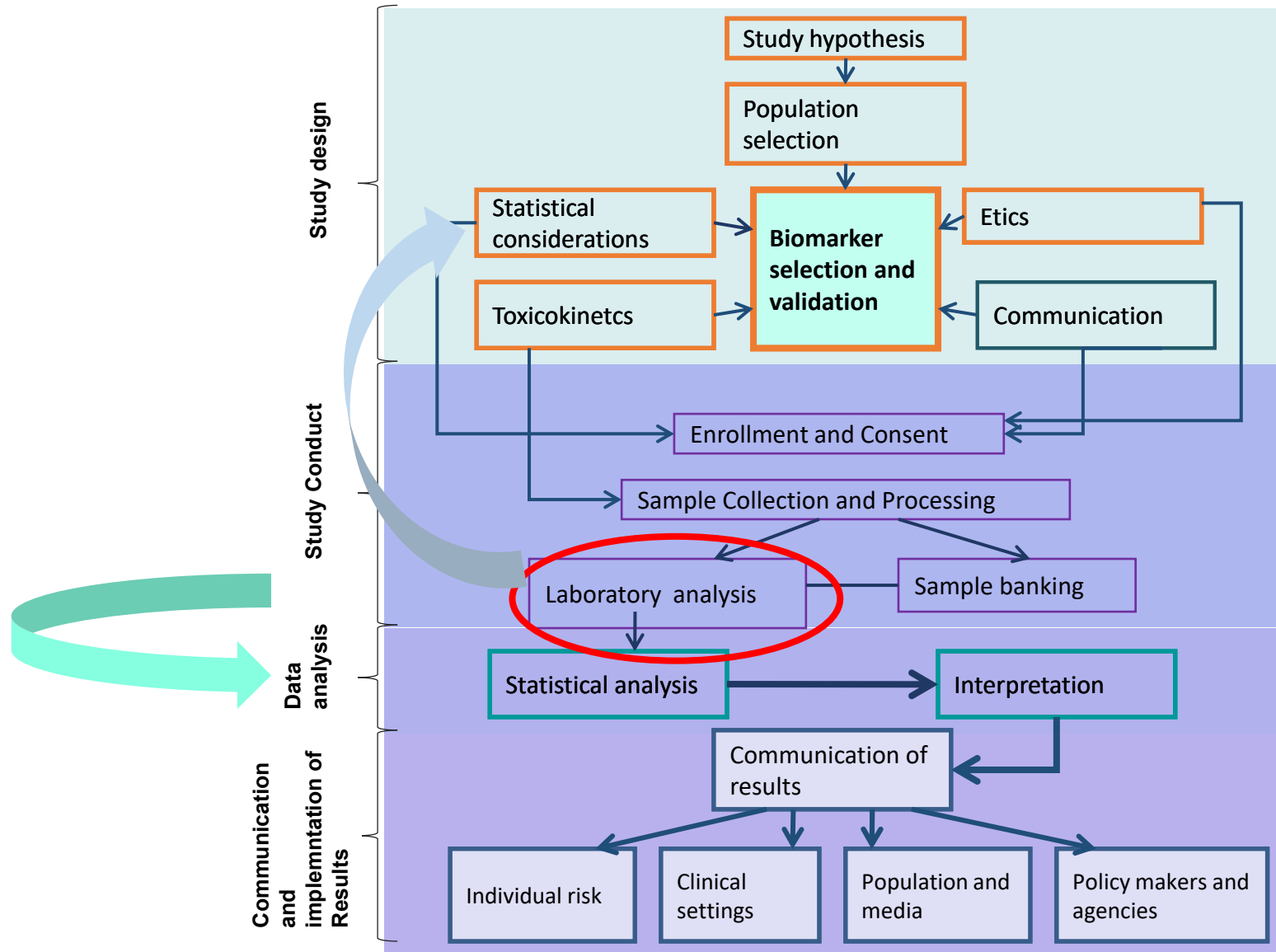
$$\text{RESULT} = \text{VALUE} \pm \underline{\text{UNCERTAINTY}}$$

Uncertainty

- Value assigned to a measurement result that characterizes how well it is known/unknown



Analytical quality objectives and planning of HBM



- SOPs (sampling and sample storage)
- Validated analytical procedures
- Trained personnel
- Day to day quality control procedures (blanks, **matrix RM materials**, QA charts, etc..)
- Calibrated equipment (**calibration RM materials**)
- External quality control (inter-laboratory comparisons, proficiency testing, key comparisons, ..)

Definition ISO/REMCO 2005

Material, sufficiently **homogenous** 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.

- *Generic term*
- *Property can be quantitative or qualitative*
- *Uses: calibration, assessment of a measurement procedure, assigning values to other materials and QC*
- *Can be used for a single purpose in a given measurement*

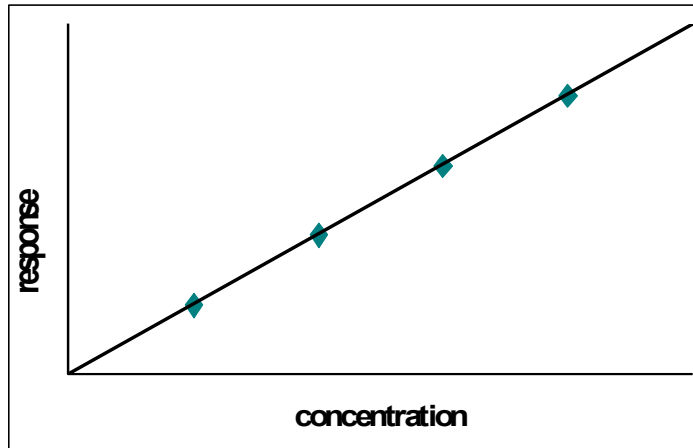
Definition ISO/REMCO 2005

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

Metrologically valid procedures: ISO Guide 34 and 35

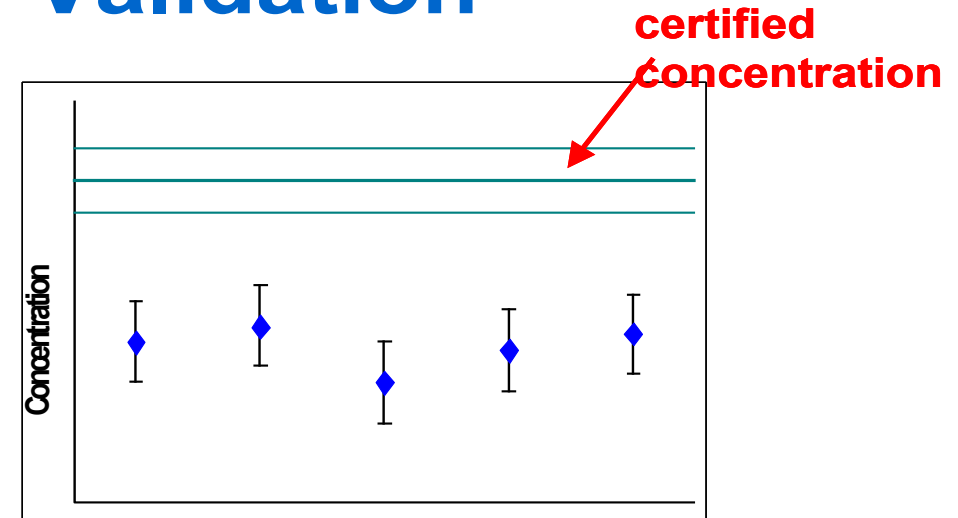
Contents in the certificate: ISO Guide 31.

Calibration



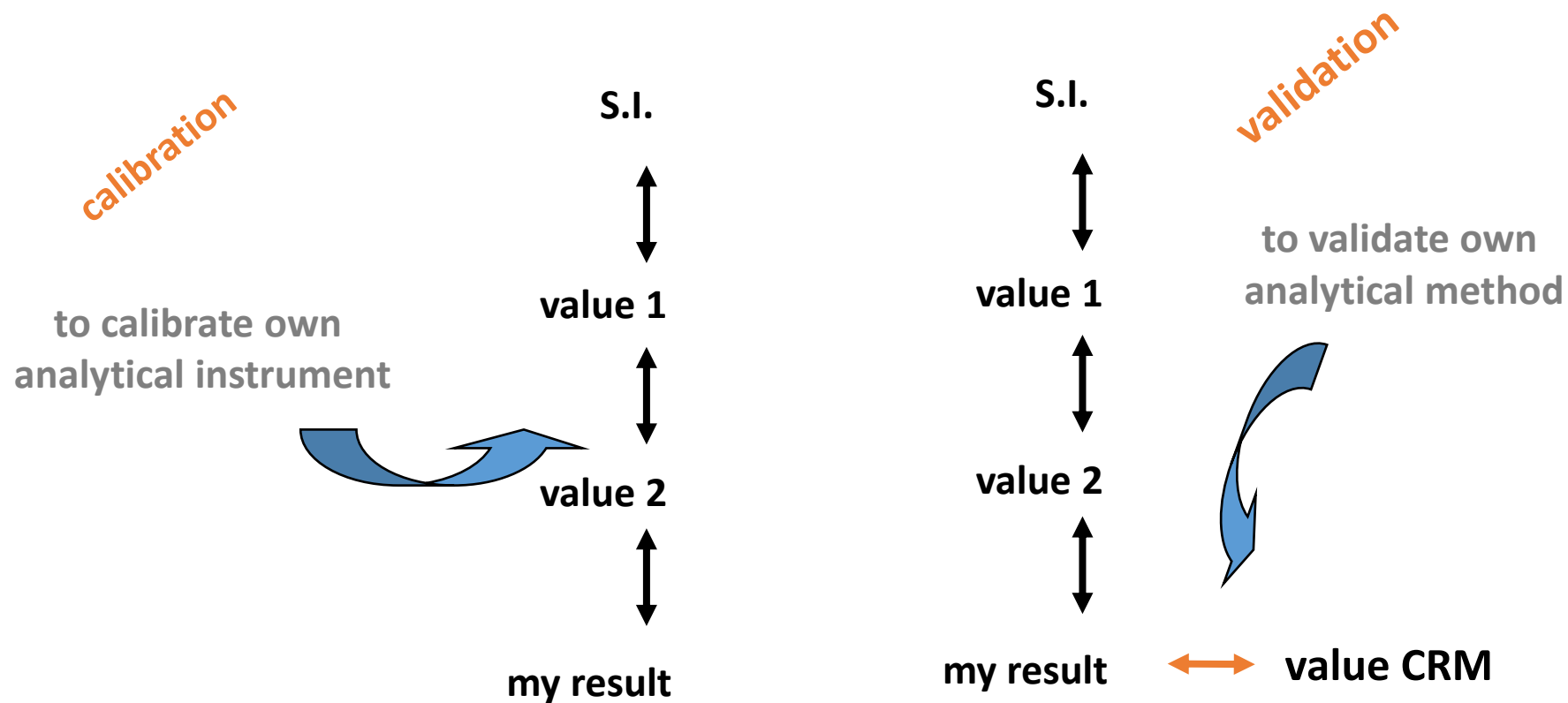
use as a matrix matched
calibrant
(direct or via working
standards)
to ensure traceability of results
to an external reference (the
CRM)

Validation



check the measurement results
in terms of validity:
is there any method specific bias ?
is there any systematic error ?

How CRMs are Used in Terms of Traceability?



Assurance of measurement comparability (I)

Certified value in CRM is:

The property value and its uncertainty


User:

$$U_c = \sqrt{U_m^2 + U_{mat}^2 + u_{CRM}^2 + \dots \dots}$$


Assurance of measurement comparability (II)

Uncertainty of the CRM is one of the strong components in the combined uncertainty of the user's results

$$U_{\text{user's results}} > U_{\text{CRM}}$$



ONLY direct matrix and concentration match of the sample and CRM (and CRM as calibrant) can be used to demonstrate accuracy and traceability

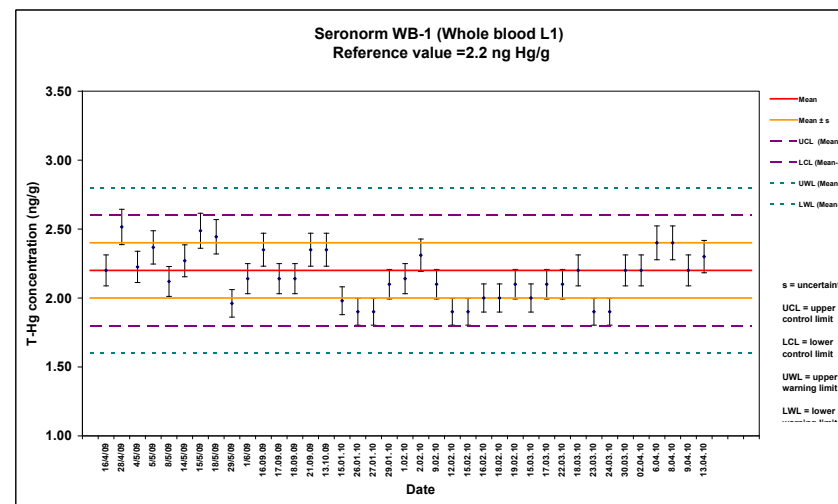
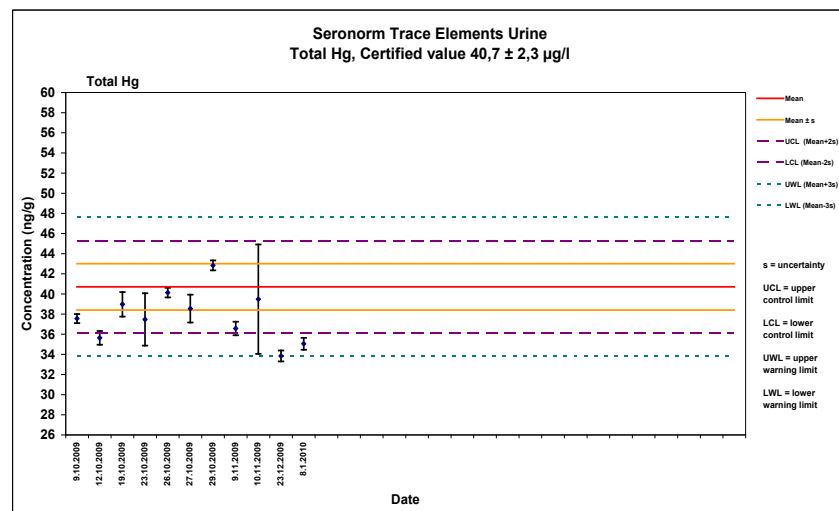
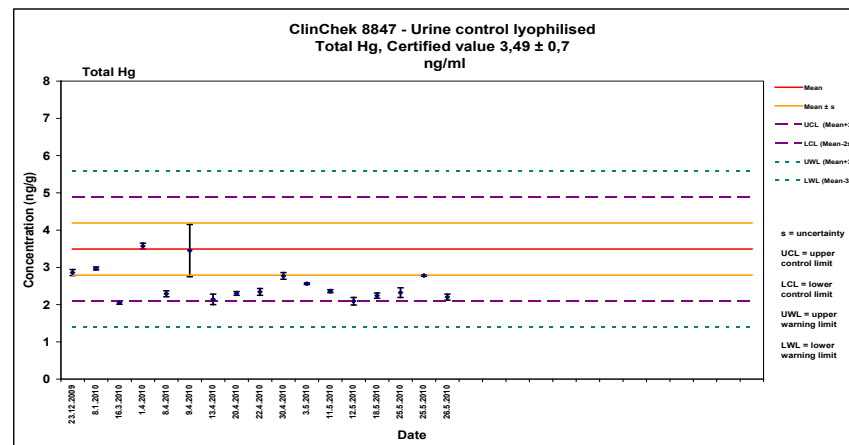
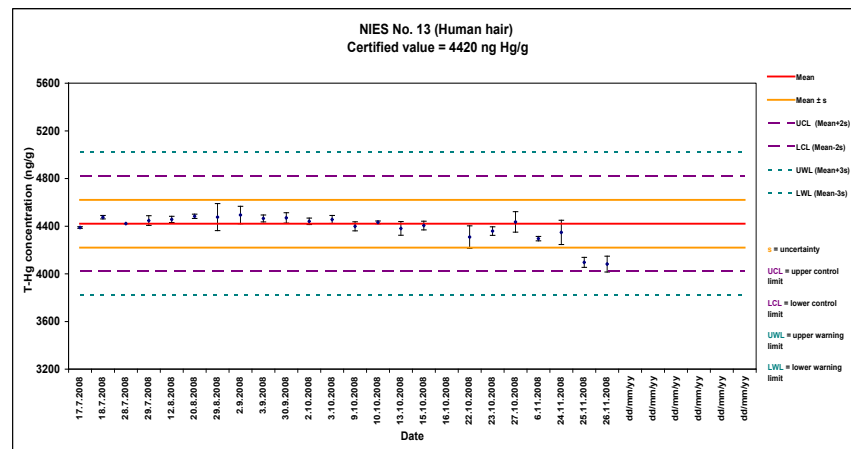


CRM producer **MUST** take intended use of CRM into consideration in the planning and preparation stages and **PROVIDE** instructions on how to establish traceability to the stated reference

QC chart



Institut "Jožef Stefan", Ljubljana, Slovenija





Knowledge

Overview

Scientific tools & databases

Publications

Reference & measurement

Selected publications

Measurements matter

European Union Reference
Laboratories

Interlaboratory comparisons

Reference Materials (RM)

RM releases

RM catalogue/ordering

User support

RM development

Useful links

Reference Materials (RM)

The JRC is one of the major developers and producers of reference materials in the world. Reference materials are reliable quality assurance tools that improve confidence in test results obtained by laboratories. They play a key role in the calibration of laboratory instruments by providing precise reference values and data.

The JRC currently provides nearly 800 different reference materials under the BCR, IRMM and ERM brands in the fields of food and feed analysis, environmental analysis, engineering and health applications. All these materials come with clear traceability statements on their certificate.

Reference materials can be ordered directly from the JRC, Geel or from one of the authorised distributors.

3.2.2 CERTIFIED FOR THE TOTAL ELEMENT CONTENT AND OTHER PROPERTIES

	Description	Substance	Metal concentrations in the reconstituted material ¹⁾ (µg/L)	
ERM-CE195	Lyophilised bovine blood	Pb Cd ²⁾	416 5.06	± 9 ± 0.15
ERM-CE196	Lyophilised bovine blood	Pb Cd ²⁾	772 12.33	± 11 ± 0.20
BCR-634	Lyophilised human blood	Pb Cd	46 1.4	± 5 ± 0.4
BCR-635	Lyophilised human blood	Pb Cd	210 6.6	± 24 ± 0.6
BCR-636	Lyophilised human blood	Pb Cd	$0.52 \cdot 10^3$ 11.6	± $0.05 \cdot 10^3$ ± 0.6

Availability: In units of lyophilised material equivalent to about 5.75 mL of bovine blood with additives kept under nitrogen in rubber stoppered vials.

BCR-634, BCR-635 and BCR-636 are available in lyophilised form in brown glass vials, containing approximately 0.6 g dry matter equivalent to 3.0 mL of fresh whole blood.

¹⁾ The sample is to be reconstituted with (5.00 ± 0.01) mL water.

²⁾ Recertified by the JRC.

	Description	Substance	Metal concentrations (µg/L)		
BCR-637	Human serum	Al	12.5	±	3.0
		Se	81	±	7
		Zn	1110	±	220
BCR-638	Human serum	Al	55	±	7
		Se	104	±	7
		Zn	1430	±	210
BCR-639	Human serum	Al	194	±	14
		Se	133	±	12
		Zn	2360	±	140

Availability: supplied in frozen form in white plastic vials containing approximately 4.5 mL serum.

Reference materials

National Institute of Standards and Technology, USA

NIST

STANDARD REFERENCE MATERIALS® CATALOGUE

NIST Offers a Comprehensive Portfolio of SRMs for

- Chemical Compositions
- Physical Properties
- Engineering Materials

Applicable for calibration, validation, method development, quality control and trueness estimation in analytical laboratories.

Health and Industrial Hygiene

Clinical Laboratory Materials (Gas, Liquid, and Solid Forms)

Cat. No.	SRM Code	Description	Unit Size
NIST955C	SRM 955C	Toxic Metals in Caprine Blood	4 Vials
NIST2668	SRM 2668	Toxic Elements in Frozen Human Urine	Set (10)
NIST2669	SRM 2669	Arsenic Species in Frozen Human Urine	Set (10)
NIST2670A	SRM 2670A	Toxic Elements in Urine Freeze-Dried	Set (4)
NIST3672	SRM 3672	Organic Contaminants in Smokers' Urine (Frozen)	5 × 10 mL
NIST3673	SRM 3673	Organic Contaminants in Non-Smokers' Urine (Frozen)	5 × 10 mL



Certificate of Analysis

Standard Reference Material[®] 2668

Toxic Elements in Frozen Human Urine

Table 1. Certified Mass Concentration Values

	Level I ($\mu\text{g/L}$)	Coverage Factor, k	Level II ($\mu\text{g/L}$)	Coverage Factor, k
Antimony			22.4 ± 1.0	1.96
Arsenic	10.81 ± 0.54	1.99	213.1 ± 4.4	2.02
Barium			254.6 ± 3.2	2.07
Beryllium			54.5 ± 2.4	2.06
Cadmium	1.056 ± 0.052	2.00	16.40 ± 0.25	2.07
Cesium	4.90 ± 0.30	2.02	221 ± 12	2.06
Chromium			27.7 ± 2.1	1.90
Cobalt	0.816 ± 0.058	1.89	51.8 ± 1.7	1.98
Copper			134.1 ± 5.4	1.97
Lead	1.234 ± 0.061	2.00	137.9 ± 3.6	2.02
Manganese			47.6 ± 3.4	2.01
Molybdenum			1687 ± 58	2.04
Nickel			115.3 ± 5.2	2.05
Vanadium	0.980 ± 0.086	1.97	48.5 ± 4.6	2.06



Certificate of Analysis

Standard Reference Material[®] 2668

Toxic Elements in Frozen Human Urine

Table 2. Reference Mass Concentration Values

	Trace Elements							
	Level I ($\mu\text{g/L}$)		Coverage Factor, k		Level II ($\mu\text{g/L}$)		Coverage Factor, k	
Antimony	0.242	\pm	0.031	1.93				
Barium	1.96	\pm	0.14	2.06				
Beryllium	1.073	\pm	0.081	1.93				
Chromium	1.08	\pm	0.31	2.09				
Copper	28.1	\pm	2.0	2.05				
Manganese	1.08	\pm	0.16	1.97				
Molybdenum	51.6	\pm	1.8	1.95				
Nickel	2.31	\pm	0.32	2.04				
Platinum	1.04	\pm	0.12	1.87	117.0	\pm	9.8	1.98
Thallium	0.719	\pm	0.029	2.15	115.2	\pm	2.8	2.00
Tin	1.69	\pm	0.14	1.91	171.0	\pm	9.0	1.96
Tungsten	1.252	\pm	0.080	2.00	62.5	\pm	1.0	2.00
Uranium	0.0340	\pm	0.0024	2.05	13.37	\pm	0.49	1.97



Certificate of Analysis

Standard Reference Material[®] 3672

Organic Contaminants in Smokers' Urine

(Frozen)

Table 1. Certified Mass Fraction Values for Hydroxylated PAHs in SRM 3672

Hydroxylated PAHs	Mass Fraction ($\mu\text{g/kg}$)		
1-Naphthol ^(a,b,c)	33.8	\pm	4.3 ^(d)
2-Naphthol ^(a,b,c)	8.57	\pm	0.16 ^(d)
9-Hydroxyfluorene ^(a,b,c)	0.331	\pm	0.077 ^(e)
3-Hydroxyfluorene ^(a,b,c)	0.420	\pm	0.018 ^(d)
2-Hydroxyfluorene ^(a,b,c)	0.854	\pm	0.015 ^(d)
4-Hydroxyphenanthrene ^(a,b,c)	0.0480	\pm	0.0045 ^(d)
9-Hydroxyphenanthrene ^(a,c)	0.959	\pm	0.061 ^(d)
3-Hydroxyphenanthrene ^(a,b,c)	0.123	\pm	0.007 ^(d)
1-Hydroxyphenanthrene ^(a,b,c)	0.133	\pm	0.014 ^(e)
2-Hydroxyphenanthrene ^(a,b,c)	0.0825	\pm	0.0007 ^(e)
1-Hydroxypyrene ^(a,b,c)	0.170	\pm	0.010 ^(e)



Certificate of Analysis

Standard Reference Material[®] 3672

Organic Contaminants in Smokers' Urine

(Frozen)

Table 2. Reference Mass Fraction Values for Selected Phthalate Metabolites in SRM 3672

Phthalate Metabolites	Mass Fraction ^(a,b) ($\mu\text{g/kg}$)	
Mono-carboxynonyl phthalate isomers ^(c)	1.92	\pm 0.06
Mono-carboxyoctyl phthalate isomers ^(d)	21.3	\pm 1.1
Mono-(2-ethyl-5-carboxypentyl) phthalate	35.2	\pm 1.7
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	24.8	\pm 0.4
Mono-(2-ethyl-5-oxohexyl) phthalate	14.9	\pm 0.4
Mono-(2-ethylhexyl) phthalate	4.13	\pm 0.15
Mono-(3-carboxypropyl) phthalate	2.99	\pm 0.20
Monobenzyl phthalate	8.37	\pm 0.18
Monoethyl phthalate	94.5	\pm 3.0
Mono-isobutyl phthalate	6.40	\pm 0.28
Mono- <i>n</i> -butyl phthalate	10.6	\pm 0.5



Certificate of Analysis

Standard Reference Material[®] 3672

Organic Contaminants in Smokers' Urine

(Frozen)

Table 3. Reference Mass Fraction Values for Selected Phenol Metabolites in SRM 3672

Phenol Metabolites	Mass Fraction ($\mu\text{g/kg}$)
Bisphenol A (BPA) ^(a,b)	3.05 \pm 0.16 ^(c)
2,5-Dichlorophenol ^(b)	1.77 \pm 0.06 ^(d)
Benzophenone-3 ^(b)	191 \pm 5 ^(d)
Methyl Paraben ^(b)	113 \pm 2 ^(d)
Ethyl Paraben ^(b)	8.12 \pm 0.20 ^(d)
Propyl Paraben ^(b)	17.6 \pm 0.3 ^(d)
Butyl Paraben ^(b)	11.1 \pm 0.2 ^(d)
Triclosan ^(b)	17.7 \pm 0.5 ^(d)



Certificate of Analysis

Standard Reference Material[®] 3672

Organic Contaminants in Smokers' Urine

(Frozen)

Table 4. Reference Mass Fraction Values for Selected VOC Metabolites in SRM 3672

VOC Metabolites	Mass Fraction ^(a,b) ($\mu\text{g/kg}$)
-----------------	--

Table 5. Reference Mass Fraction Values for Additional Analytes in SRM 3672

Analytes	Mass Fraction ^(a,b) (mg/kg)	k
Creatinine	734 \pm 5	2.07
Nicotine ^(c)	0.731 \pm 0.018	2.16
Ibuprofen ^(c)	0.122 \pm 0.005	2.16
Caffeine ^(c)	2.65 \pm 0.05	2.16
Cotinine ^(c)	1.09 \pm 0.02	2.16
Theobromine ^(c)	3.31 \pm 0.09	2.16
3-Hydroxycotinine ^(c)	3.46 \pm 0.09	2.16

[Home](#) > [Data / Resources](#) > [Database / Tool](#) > NIES-CRMs

▶ [このページを日本語で読む](#)

NIES CRMs

Environmental Certified Reference Materials (CRMs) are utilized to evaluate new analytical methods and to control the accuracy of pretreatment and instrumental analyses.

National Institute for Environmental Studies (NIES) have been preparing and distributing environmental and biological CRMs since 1980.

We have provided 52 countries with thousands of bottles for the past 20 years.

At present, 15 CRMs are available (including 1 CRM which cannot be sent overseas).



National Institute for Environmental Studies

Certified Reference Material No.13

Human Hair

TABLE 1

Certified values of constituents in NIES CRM No.13 Human Hair

Constituent	Concentration ^a	Analytical Methods ^b
Methyl Hg	3.8 ± 0.4	3,13,14,15
Total Hg	4.42 ± 0.20	2,3,4,5,10
Cd	0.23 ± 0.03	1,8,9,10
Cu	15.3 ± 1.3	1,5,7,8
Pb	4.6 ± 0.4	1,8,10,12
Sb	0.042 ± 0.008	1,5,8,10
Se	1.79 ± 0.17	1,5,6,8,9,10,11
Zn	172 ± 11	1,5,7,8,10

a Certified value \pm uncertainty expressed as $\mu\text{g/g}$ dry weight. Samples should be dried at 85 °C for 4 hrs in a conventional electric oven and then cooled in a silica gel dessicator at room temperature before weighing.

National Institute for Environmental Studies

Certified Reference Material No.18

“Human Urine”

TABLE 1 Certified and Reference Values for NIES CRM No. 18 Human Urine¹

	Unit	Certified Value	analytical methods ²
Total arsenic	mg/L	0.137 ± 0.011	a,b,c,d,e,f
Arsenobetaine	mg/L as As	0.069 ± 0.012	g,h
Dimethylarsinic acid	mg/L as As	0.036 ± 0.009	g,i
Total selenium	mg/L	0.059 ± 0.005	d,e,f,j
Total zinc	mg/L	0.62 ± 0.05	f,k,l
	Unit	Reference Value	
Total copper	mg/L	0.010	
Total lead	mg/L	0.0011	

Hg - List of matrix RM and CRMs



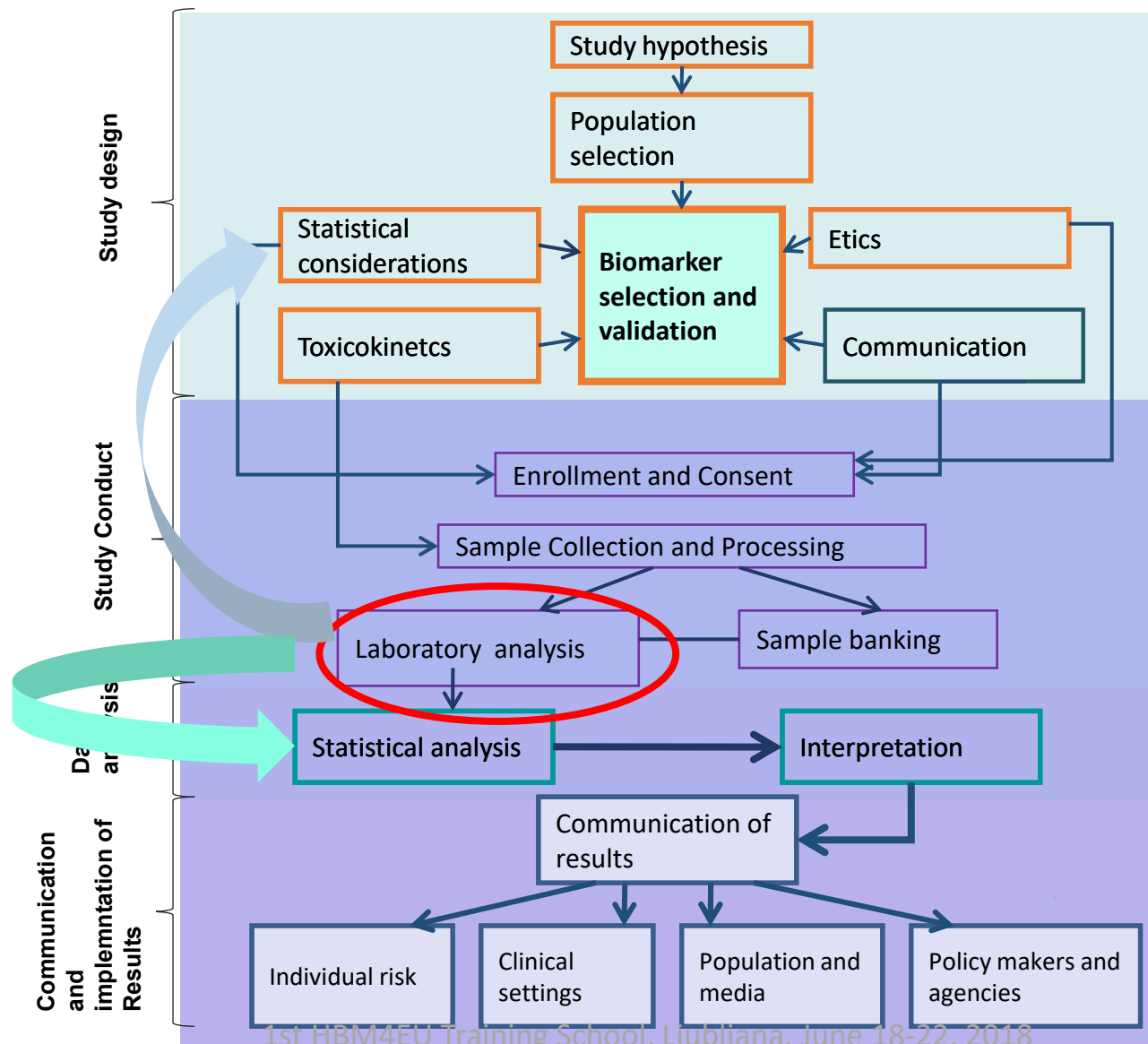
RM/CRM	Matrix	Analyte	Producer
IAEA-85	hair	Hg	IAEA Analytical Quality Control Services
IAEA-86	hair	Hg	IAEA Analytical Quality Control Services
IAEA-86	hair	MeHg	IAEA Analytical Quality Control Services
BCR-397	hair	Hg, MeHg	IRMM-Institute for Ref Materials and Measurem
ERM-DB001	hair	Hg	IRMM
GBW 09101 (CRM GBW 07601)	hair	Hg	School of Public Health for Beijing Medical Univ. Office of CRMs
NIES No 13	hair	Hg, MeHg	NIES, National Institute for Enviromental Studies
NIES No 5	Hair	Hg	NIES, National Institute for Enviromental Studies
SRM 966	Bovine blood	Hg, IHg., MeHg	NIST, USA
SRM 955c, level 3	Caprine blood	THg, IHg, EtHg, MeHg	NIST, USA
SRM 3668	Frozen urine	THg (2 levels)	NIST, USA

Preferred: commercially available from NMIs:

- SRM 3133 - Mercury (Hg) Standard Solution
- SRM 3177 - Mercuric Chloride Standard Solution

Gravimetrically prepared – Caution when prepared from Hg salts!

Analytical quality objectives and planning of HBM



- Minimum quality requirements for concentration ranges should be defined in health related studies (LOD, LOQ, uncertainty)
- QA/QC procedures MUST be in place
- Only validated analytical methods – quality requirements MUST be agreed before samples are to be analyzed
- Proper use of calibration and matrix matched matrix RMs is required: note the difference between the fresh vs. freeze dried samples
- Regular participation in ILC (ICI/EQUAS or similar)
- Regular QC charts is mandatory

References

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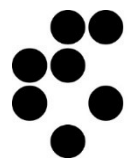
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Speaker's information

Prof. Milena Horvat is the Head of the Department of Environmental Sciences at the Jožef Stefan Institute and a Dean of the International Postgraduate School Jožef Stefan. By basic training she is an analytical chemist. She coordinated the implementation of the Slovenian HBM and several research project in the domain of environment and health studies. Within the HBM4EU IJS is a chemical group leader for Cd and involved in Training activities. WP2.



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