

Towards the harmonis(z)ation of immunoassays

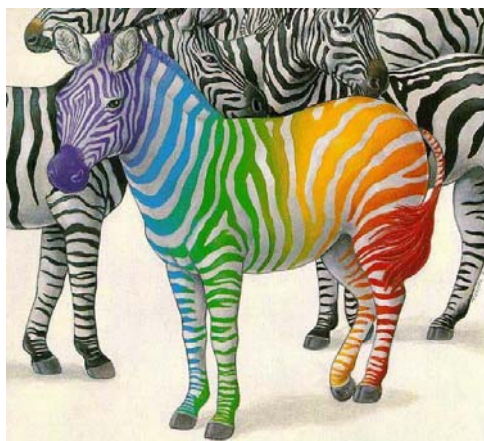
Endocrinology Theme Day



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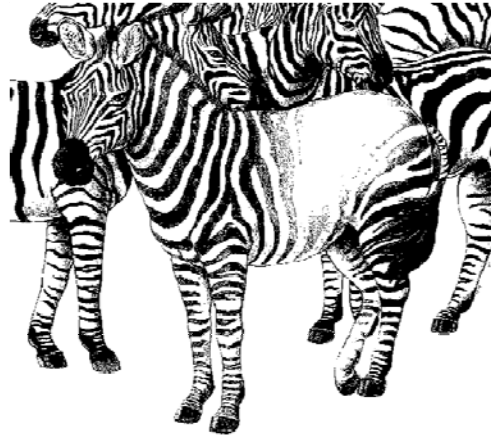
Immunoassays are different!



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No, they are'nt!



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AACB Golden Jubilee



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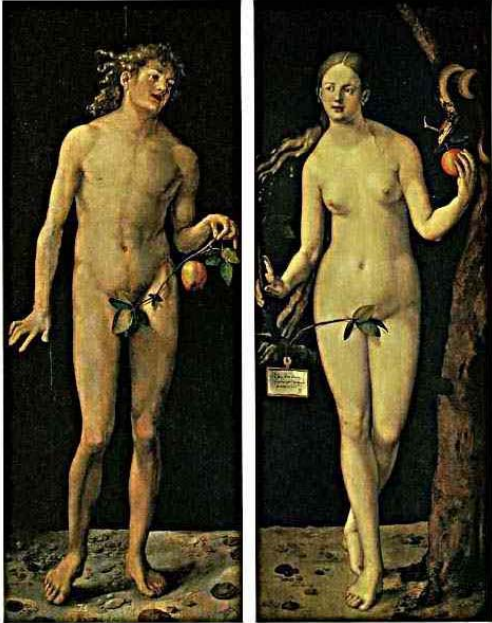
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Harmonisation "Gray" Jubilee?



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Back into history



Insulin

R. S. Yalow and S. A. Berson. 1959. "Assay of Plasma Insulin in Human Subjects by Immunological Methods." Nature 184, 1648-1649.

Still not standardised!



The Nobel Prize in Physiology or Medicine 1977,
Rosalyn Yalow "for the development of
radioimmunoassays of peptide hormones".

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Standardisation?

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Standardisation? Harmonisation?

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Traceability?

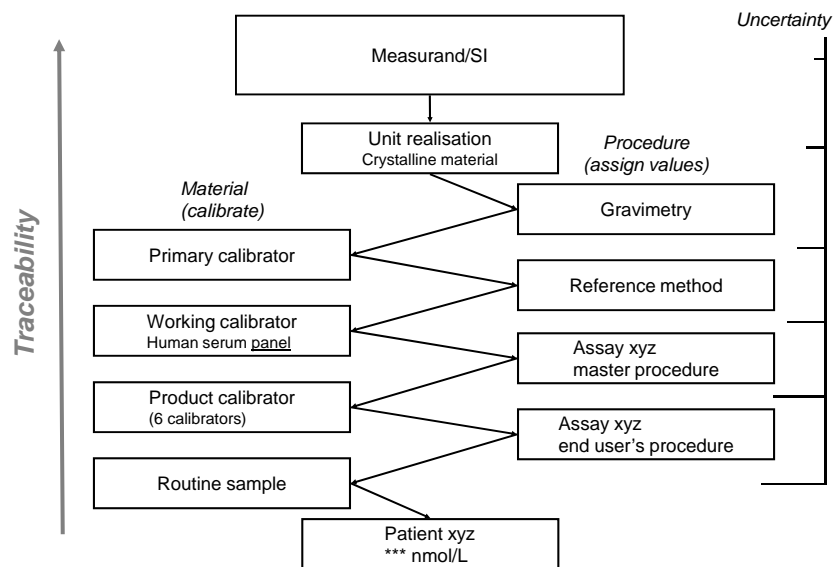
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Reference measurement system: ISO 17511

Element	Organization	Task
SI-Unit	Conférence Générale des Poids et Mesures (CGPM)	Establishment of a coherent system of units (mol)
Component (Analyte)	IFCC	Definition of the relevant component
Reference material	National Metrology Institutes; IRMM, NIST	Realisation of SI units: Production and/or certification
Reference measurement procedure (RMP)	Reference laboratory or other competent analytical laboratory	Development and validation of the procedure
Reference laboratory	No representative organization ("Networks")	Application of RMP
Reference measurement system	JCTLM	Endorsement

Reference measurement system: ISO 17511



Reference measurement system

Regulatory environment

ISO 15194

Requirements for certified reference materials and the content of supporting documentation

ISO 15193

Requirements for content and presentation of reference measurement procedures

ISO 15195

Requirements for reference measurement laboratories

Reference measurement system



Reference methods/measurement procedures

Reference materials

Nominate at Joint Committee for Traceability in Laboratory Medicine

→ www.bipm.org/jctlm/

Reference laboratory

Accreditation

External quality assessment ("RELA" Bonn)

→ www.dgkl-rfb.de:81 DGKL

JCTLM



Database of higher-order reference materials,
measurement methods/procedures and services



Bureau International des Poids et Mesures

JCTLM Database
Laboratory medicine and *in vitro* diagnostics

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JCTLM database: Laboratory medicine and *in vitro* diagnostics

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- General information
- List of reference materials no longer listed in the JCTLM Database
- JCTLM Database Leaflet
- Contact us

▼ JCTLM

- Joint Committee for Traceability in Laboratory Medicine (JCTLM)
- JCTLM Working Group 1
- JCTLM Working Group 2

▼ Analyte keyword search for reference materials, measurement methods/procedures and services

Type an analyte name in part or full, e.g. cholesterol

Refine search by analyte category:

Refine search by matrix category:

Please select your requirement :

- Higher-order reference materials
- Reference measurement methods/procedures
- Reference measurement services

<http://www.bipm.org/jctlm/>

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Harmonisation – “New kid in town”

Harmonization.net

Clinical Laboratory Test Harmonization

AACC

Home About Education Committees

Steering Committee

The Steering Committee is responsible for overall guidance of the implementation of the recommended harmonization processes and for generating international collaborations with other organizations to create the infrastructure for harmonization. This committee will rely on the three task forces to assist in developing processes and tools needed for the infrastructure to achieve the goal of improving harmonization. [Learn More](#)

The goal for each task force is to develop the technical processes needed for implementation and to recommend them to the Steering Committee. Task forces will be dissolved as the infrastructure is created and the operation of the Harmonization Oversight Group commences to address harmonization of specific measurands.

Task Force for Planning the Harmonization Oversight Group This task force will develop procedures for operation of the Harmonization Oversight Group and its management of harmonization activities.	Task Force for Developing Technical Measurands This task force will create a toolbox of well developed processes as a starting point for use by a Harmonization Implementation Group.	Task Force for Developing Checklists This task force will develop checklists for use by the Harmonization Oversight Group in the prioritization process and by a Specialty Work Group in the assessment of priority and feasibility for harmonization.
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Phone: (800) 892-1400 | Fax: (202) 887-5093

<http://www.harmonization.net/Pages/default.aspx>

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Tribute

Cali JP

An idea whose time has come. Clin Chem **1973**;19:291-3.



Tietz NW

A model for a comprehensive measurement system in clinical chemistry. Clin Chem **1979**; 25:833-9.

Tribute



Siekmann L et al.

Zur gas-chromatographisch-massenspektrometrischen Bestimmung von Steroidhormonen in Körperflüssigkeiten unter Verwendung eines Multiple Ion Detectors (Fragmentographie)

Z Anal Chem **1970**;252:294-8.

Tribute



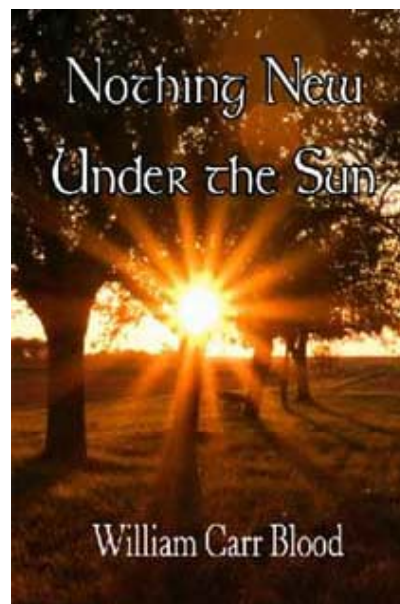
Björkhem I et al.
Method development, application & concepts

**Serum-cholesterol determination by mass
fragmentography. Clin Chim Acta 1974;54:185-93.**

**Accuracy of some routine method used in clinical
chemistry as judged by isotope dilution-mass
spectrometry. Clin Chem 1981;27:733-5.**

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Reference measurement systems

Some “points of care”



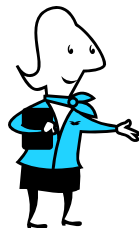
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Metrology



So, it is about rain and thunderstorms?



Oh, sorry these terms!
It's *metrology*, not
Meteorology!



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Metrology

The component (analyte) in the measurand

Measurement: “Process of experimentally obtaining one or more quantity values that can reasonably be attributed to a quantity”

Quantity [1]

property of a phenomenon, body, or substance, to which a number can be assigned with respect to a reference

Quantities are designated in laboratory medicine by the format “system–component (analyte); kind of quantity” (for example, serum–cortisol; amount-of-substance concentration equal to $x \mu\text{mol/L}$).

Measurand [1]

quantity *intended* to be measured

[1] JCGM 200:2008. International vocabulary of metrology – Basic and general concepts and associated terms (VIM). International Bureau of Weights and Measures (BIPM); Joint Committee for Guides in Metrology (JCGM): Paris, 2008 (electronic document freely available at: <http://www.bipm.org/en/publications/guides/vim.html>).

Component

S-creatinine



Alkaline picrate active substances! (Jaffe)



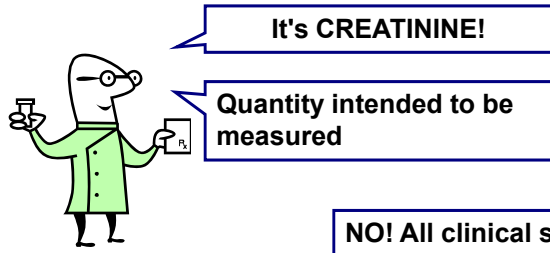
Creatinine! (Enzymatic)



I knew it was thunderstorms!

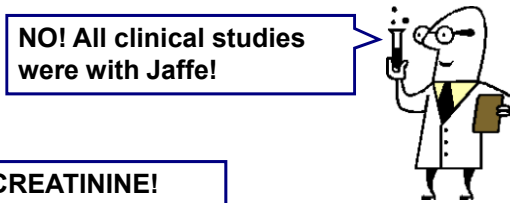


Component

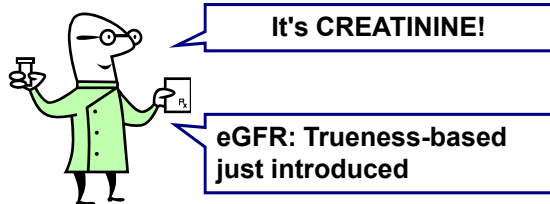


It's CREATININE!

Quantity intended to be measured




NO! All clinical studies were with Jaffe!



It's CREATININE!

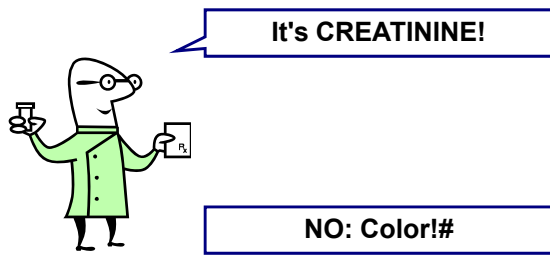
eGFR: Trueness-based just introduced



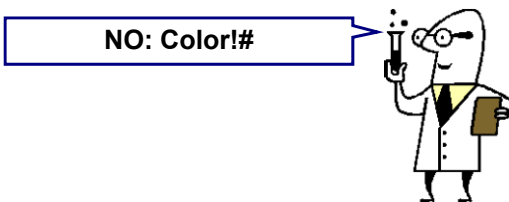
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Component




It's CREATININE!



NO: Color!#

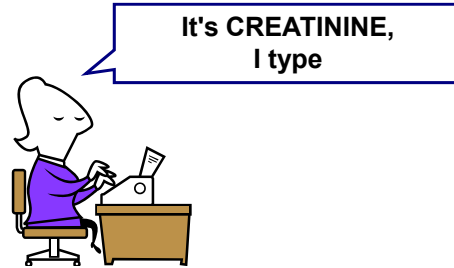
#C51-P_ACVotingDraft-August 2010 However, because the creatinine concentration cannot be directly measured, the absorbance of a colored reaction product between creatinine and alkaline picrate is measured. **In this case, the color is the component**, the absorbance at a given wavelength is the kind of quantity, and the system is serum.



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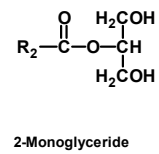
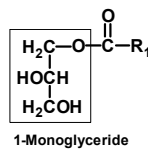
Component



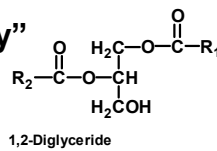
Component(s)

Example: Triacylglycerides (TGs)

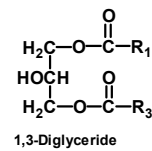
TGs have the component glycerol in common



→ Component “family”

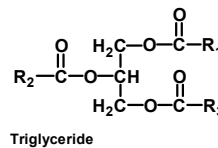


→ Measurement?



→ Standard?

→ Unit?



Component(s)

Triacylglycerides: Surrogate component glycerol

Reference and routine procedure measure the same component = glycerol

Standard

Tripalmitin

Correct unit

mmol/L **NOT** mg/dL, because of unknown composition in sample

Caution

Some use for the conversion mmol/L \leftrightarrow mg/dL the MW of tripalmitin, others MW of "average of TGs"
→ Standardisation problems, but not recognised: small difference

Component(s) – Mixture analysis!

Medical requirement for mixture analysis

Each component of the mixture should contribute significantly to the assay's diagnostic application

Analytical requirement for mixture analysis

Analytical procedures should measure the components of the mixture "equimolar"

Can be achieved by defining a "quasi surrogate component" in the measurand

Equimolarity to the diagnostic relevant extent (small variations in mixture content in individual samples should be outweighed by diagnostically important changes of the overall concentration of the mixture in health and disease)

Traceability – To which extent?

Analytical quality specifications

Tonks DB

A study of the accuracy and precision of clinical chemistry determinations in 170 Canadian laboratories.

Clin Chem 1963;9:217-33.

Harris E

Cotlove E, Harris EK, Williams GZ. Components of variation in long term studies of serum constituents in normal subjects. III. Physiological and medical implications. Clin Chem 1970;16:1028-32.



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Analytical quality specifications

Hierarchy of concepts#

- Analytical performance of *state-of-the-art* measurement methods (**bottom**)
- Opinion of *experts* or *expert groups*
- **Biological variation** data (reference intervals and within- and between subject variation)
- *Questionnaires to clinicians/physicians*
- Specific *clinical outcome* (**top**)

#Petersen PH, Fraser CG, Kallner A, Kenny D. Strategies to set global quality specifications in laboratory medicine. Scand J Clin Lab Invest 1999;59:475-585.

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Specifications for routine

Biological variation concept

Concept of *Gowans*#:

$$\begin{array}{l} \text{CV}_{\text{rou}} = 0.52 \text{ CV}_{\text{g}} \\ \text{B}_{\text{rou}} = 0.25 \text{ CV}_{\text{g}} \end{array} \longrightarrow \text{Diagnosis}$$

CV_{g} = “group” biological variation

#Gowans EM, Petersen PH, Blaabjerg O, Hørdler M. Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area. *Scand J Clin Lab Invest* 1988;48:757–64.

Specifications for routine

Biological variation concept

Concept of *Harris* [1] and *Petersen* [2]:

$$\begin{array}{l} \text{CV}_{\text{rou}} = 0.5 \text{ CV}_{\text{within}} \\ \text{B}_{\text{rou}} = 0.33 \text{ CV}_{\text{within}} \end{array} \longrightarrow \text{Monitoring}$$

$\text{CV}_{\text{within}}$ = within-subject biological variation

[1] Harris EK. Statistical principles underlying analytic goal-setting in clinical chemistry. *Am J Clin Pathol* 1979;72(2 Suppl):374–82.

[2] Petersen PH, Fraser CG, Westgard JO, Larsen ML. Analytical goal-setting for monitoring patients when two analytical methods are used. *Clin Chem* 1992;38:2256–60.

Specifications for reference & uncertainty

Reference specifications

→ Cascade down from routine#

$$\left. \begin{array}{l} CV_{\text{ref}} = 0.5 CV_{\text{rou}} \\ B_{\text{ref}} = 0.33 B_{\text{rou}} \end{array} \right\} \text{Diagnosis/monitoring}$$

Uncertainty of primary standards

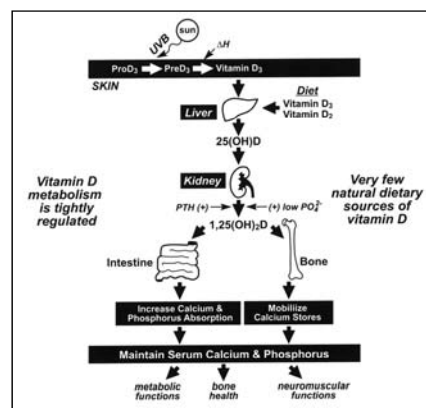
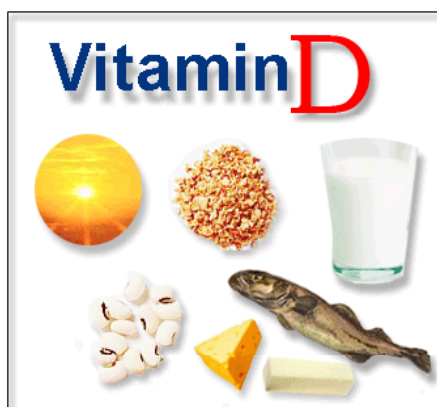
→ Cascade down from reference

$$U_{\text{rm}} = 0.33 B_{\text{ref}}$$

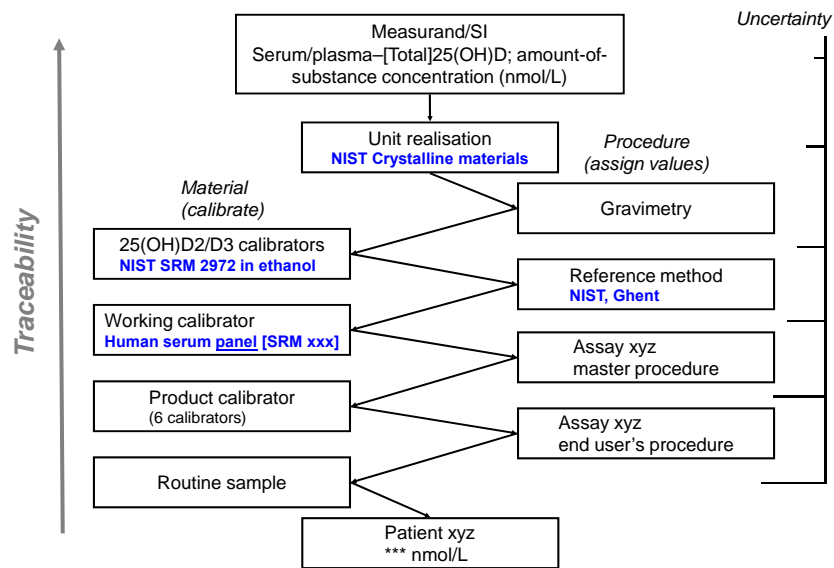
#Stöckl D, Sluss PM, Thienpont LM. Specifications for trueness and precision of a reference measurement system for serum/plasma 25-hydroxyvitamin D analysis. Clin Chim Acta 2009;408:8-13.

→ Today, no general consensus on this model!

Example 1 – 25OHD



Reference measurement system 25OHD



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Measurand

Measurand (units)

[Total] serum/plasma 25(OH)D (nmol/L)

Components

25(OH)D2

25(OH)D3

→ Mixture analysis

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Which unit?

Unit for 25(OH)D

nmol/L (“equimolar measurement”)

Why nmol/L and not ng/mL

Calculation example

10 ng/mL 25(OH)D ₂	24.2 nmol/L
10 ng/mL 25(OH)D ₃	25.0 nmol/L
20 ng/mL 25(OH)D	= 48.4 nmol/L?
	= 50 nmol/L?
	= 49.2 nmol/L?

- > Not interchangeable
- > Conceptually important

Specifications for complete system

Proposal#

Hold the balance between “desirable” Q-goals – “state-of-the-art” performance – certification capabilities

Specifications based on “diagnosis model”

Routine measurements	CV: 10% Bias: 5%
Reference measurements	CV: 5% Bias: 1.7%
Uncertainty primary standards	U: 0.6%

Caution: Stable imprecision and bias should be ~1/2 of the limit to achieve required quality in average!

#Stöckl D, Sluss PM, Thienpont LM. Clin Chim Acta 2009;408:8-13.

Reference material – Calibrator

Standard material

NIST SRM 2972

Uncertainty 1.6%#

#Certificate of analysis, Standard Reference Material 2972:25-hydroxyvitamin D2 and D3 calibration solutions. Gaithersburg, MD: Standard Reference Materials Program, NIST; 2009.

Desired specification

Uncertainty primary standards	U: 0.6%

Reference material – Serum-based

Certified Concentration Values (\pm uncertainty *U*) for Vitamin D Metabolites in SRM 972 (nmol/L)

Certified Concentration Values (\pm uncertainty *U*) for Vitamin D Metabolites in SRM 972 (ng/mL)

Level 1 (some D2 and epi)				Level 1 (some D2 and epi)			
		nmol/L	%		ng/mL	%	
25OHD3	59.6	\pm 2.1	3.5	25OHD3	23.9	\pm 0.8	3.3
Total	59.6	\pm 2.1	3.5	Total	23.9	\pm 0.8	3.3
Level 2 (some epi)				Level 2 (some epi)			
25OHD2	4.1	\pm 0.2	4.6	25OHD2	1.7	\pm 0.1	4.7
25OHD3	30.8	\pm 1.5	4.9	25OHD3	12.3	\pm 0.6	4.9
Total	34.9	\pm 1.5	4.3	Total	14.0	\pm 0.6	4.3
Level 3 (some epi)				Level 3 (some epi)			
25OHD2	64.1	\pm 4.8	7.5	25OHD2	26.4	\pm 2.0	7.6
25OHD3	46.2	\pm 2.8	6.1	25OHD3	18.5	\pm 1.1	5.9
Total	110.3	\pm 5.6	5.0	Total	44.9	\pm 2.3	5.1
Level 4 (high epi)				Level 4 (high epi)			
25OHD2	6.8	\pm 0.6	9.0	25OHD2	2.4	\pm 0.2	8.8
25OHD3	82.3	\pm 2.0	2.4	25OHD3	33	\pm 0.8	2.4
Total	88.1	\pm 2.1	2.3	Total	35.4	\pm 0.8	2.3

U somewhat high: We would be better served with <2%

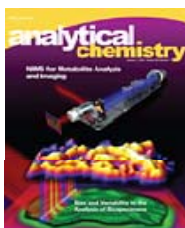
Note: SRM 972 not commutable with IAs. Therefore, new SRM 972a AND panel of native sera in preparation!

Reference measurement procedure



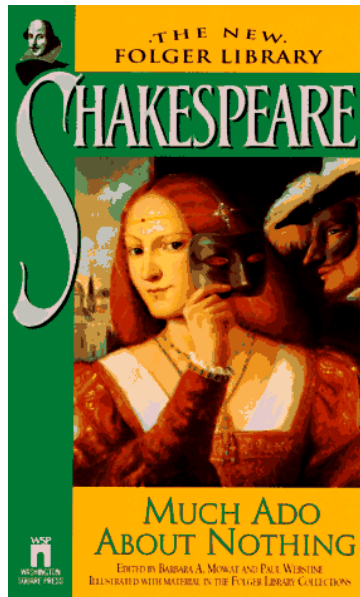
Stepman HC, Vanderroost A, Van Uytfanghe K, Thienpont LM. Candidate reference measurement procedures for serum 25-hydroxyvitamin D3 and 25-hydroxyvitamin D2 by using isotope-dilution liquid chromatography-tandem mass spectrometry. Clin Chem 2011;57:441-8.

Reference measurement procedure



Tai SS-C, Bedner M, Phinney KW. Development of a candidate reference measurement procedure for the determination of 25-hydroxyvitamin D(3) and 25-hydroxyvitamin D(2) in human serum using isotope-dilution liquid chromatography-tandem mass spectrometry. Anal Chem 2010;82:1942-8.

What do we need more?



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Reference measurement system 25OHD



Vitamin D Standardization Program (VDSP)

Goal: To improve the detection, evaluation and treatment of vitamin D malnutrition by making serum total 25-hydroxyvitamin D measurements accurate & comparable over time, location & laboratory procedure.



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Reference measurement systems

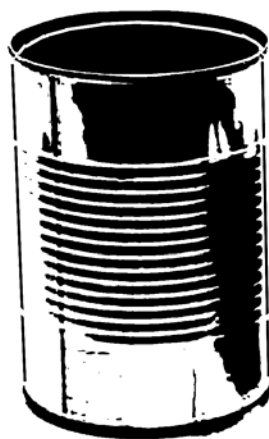
For the low-hanging fruits –
All sunshine?



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Beware of common snails



By Dietmar Stöckl
ST Consulting

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Tribute to somebody absent



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The regulation snail



Cali JP. An idea whose time has come. Clin Chem 1973;19:291–3.

“My personal opinion is that it is almost certain that the Product Standards soon to be promulgated by the Food and Drug Administration with regard to the labeling requirements of clinical kits, chemicals, and devices will, where applicable, somehow relate to and (or) require the use of referee methods (or state-of-the-art interim methods where referee methods have not yet been developed) to provide the baseline against which other methods or products will be assessed”.

Today, FDA approval is still by comparison with a predicate assay

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The standardisation snails



Björkhem I, et al. Assay of cortisol with a radioimmunoassay method calibrated by isotope dilution-mass spectrometry. Scand J Clin Lab Invest 1983;43:433-7.

"The calibration standards used in the RIA method ... were replaced by a series of human serum samples, in which the concentration of cortisol had been determined by the reference ID-MS method".

More and more industry standard, but still heavily discussed by the scientific community

The "harmonisation" snail



Carey RN, Wold S, Westgard JO. Principal component analysis: an alternative to "referee" methods in method comparison studies. Anal Chem 1975;47:1824-9.

Lawton WH, et al. Statistical comparison of multiple analytic procedures - application to clinical-chemistry. Technometrics 1979;21:397-409.

Rymer JC, et al. A new approach for clinical biological assay comparison and standardization: application of principal component analysis to a multicenter study of twenty-one carcinoembryonic antigen immunoassay kits. Clin Chem 1999;45:869-81.

Still heavily discussed by many

The goal snail



Tonks DB. A study of the accuracy and precision of clinical chemistry determinations in 170 Canadian laboratories. Clin Chem 1963;9:217-33.

Kenny D, Fraser CG, Hyltoft Petersen P, Kallner A. Strategies to set global quality specifications in laboratory medicine, Stockholm, 24-26 April 1999. Consensus agreement. Scand J Clin Lab Invest 1999;59:585.

Still not fully appreciated

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The commutability snail*



*Also known under the name "matrix-effect" snail

Charles F. Fasce, Jr., Robert Rej, William H. Copeland, and Raymond E. Vanderlinde. A Discussion of Enzyme Reference Materials: Applications and Specifications. Clin Chem 1973;19:5-9.

Stöckl D, Thienpont LM. The combined-target approach: a way out of the proficiency testing dilemma. Arch Pathol Lab Med 1994;118:775-6.

Many still use calibration/trueness control materials not tested for commutability

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The uncertainty snail



ISO/IEC Guide 98:1995. Guide to the expression of uncertainty in measurement (GUM). International Organization for Standardization: Geneva, 1995.

CLSI C51?

ISO 25680?

Still no consensus in CC/LM

Reverse-gear snails



Equivalent quality control

General observation of snails

Spring B. Health Decision Making: Lynchpin of Evidence-Based Practice. Med Decis Making 2008;28;866-74.

The Institute of Medicine notes that a chasm persists between what we know scientifically and what we apply to health care practice.¹

One estimate is that uptake of new medical discoveries into clinical practice still only proceeds at the rate of 14% uptake after 17 years.²

¹Institute of Medicine. Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC: National Academy of Science Press; 2001.

²Balas EA, Boren SA. Yearbook of Medical Informatics: Managing Clinical Knowledge for Health Care Improvement. Stuttgart, Germany: Schattauer Verlagsgesellschaft mbH; 2000.

DIGRESSING



DIGRESS, v.i. [L., to step. See Grade.]

1. Literally, to step or go from the way or road; hence, to depart or wander from the main subject.

Example 2 – TSH (complex mixture analysis)



Thienpont LM, Van Houcke SK.
Traceability to a common standard for protein
measurements by immunoassay for in-vitro diagnostic
purposes. Clin Chim Acta 2010;411:2058-61.

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Ekins

PURIST

“Insofar as the antigenic substances present in standards or test samples are dissimilar and/or molecularly heterogeneous, an immunoassay is invalid, and the results it yields have no universal significance.



Attempts to standardise “analytically-invalid” immunoassays inevitably fail. It is thus impossible to “measure TSH”. The only long-term solution to this problem is the development of assay systems measuring individual components of such heterogeneous mixtures”.

Ekens R. Immunoassay standardization. Scand J Clin Lab Invest 1991;51 Suppl 205:33-46.

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Ekins

PRAGMATIST

“It is nevertheless possible to visualise circumstances in which an assay system, though analytically invalid in the strictest sense, responds only to a particular atomic group common to the molecules of substances differing in overall structure (for example, the protein moiety in TSH)”.



Ekins R. Immunoassay standardization. Scand J Clin Lab Invest 1991;51 Suppl 205:33-46.

TSH – Pragmatic approach#

Reference measurement system for mixture analysis

Continuum from discovery to translation into SI

Different needs at different stages of the continuum

Dynamic, updatable according to scientific progress and technical possibilities

Definition of the measurand commensurate with its realisation by a measurement standard (and vice versa) at any stage in the continuum

#Thienpont LM, Van Houcke SK. Traceability to a common standard for protein measurements by immunoassay for in-vitro diagnostic purposes. Clin Chim Acta 2010;411:2058-61.

TSH – Pragmatic approach

Component(s) in the measurand

Currently, not yet formally defined

We propose to define the component(s) as
“hTSH, intact, total, glycosylation encountered in diagnostic applications which should be specified”

NOTE

Requires **equimolarity** of measurement to a diagnostic relevant extent

“Surrogate component-mixture” in the measurand

Epitopes at invariable peptide sequences that immunoassays should recognize

TSH – Pragmatic approach

“Surrogate” reference measurement procedure

“All-procedure trimmed mean” of a method comparison on a panel of native sera with several immunoassays throughout the continuum.

Note: Sufficient correlation is required

Traceability

Remains established by transfer of the IU of the WHO 80/558 standard to a panel of native sera (all-trimmed mean of a method comparison study)

Continuity is ensured by transfer of the IU from the first panel to the follow-up panels via consecutive method comparison studies

Harmonisation – TSH first?

The screenshot shows the website [Harmonization.net](http://www.harmonization.net) with the AACC logo. The navigation menu includes Home, About, Education, and Committees. The main content area is titled "Steering Committee" and describes its role in guiding harmonization processes. Below this, three task forces are listed:

- Task Force for Planning the Harmonization Oversight Group:** This task force will develop procedures for operation of the Harmonization Oversight Group and its management of harmonization activities.
- Task Force for Developing Technical Measurands:** This task force will create a toolbox of well developed processes as a starting point for use by a Harmonization Implementation Group.
- Task Force for Developing Checklists:** This task force will develop checklists for use by the Harmonization Oversight Group in the prioritization process and by a Specialty Work Group in the assessment of priority and feasibility for harmonization.

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<http://www.harmonization.net/Pages/default.aspx>

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AACC – Harmonisation

The screenshot shows the website [Harmonization.net](http://www.harmonization.net) with the AACC logo. The navigation menu includes Home, About, Education, and Committees. The main content area is titled "Harmonisation Oversight Group#" and lists its responsibilities:

Harmonisation Oversight Group#

Management of the process including:

Receipt of proposed candidate measurands for consideration

Prioritization of measurands

Oversight of the implementation of harmonisation schemes for different measurands

Communication with all stakeholders

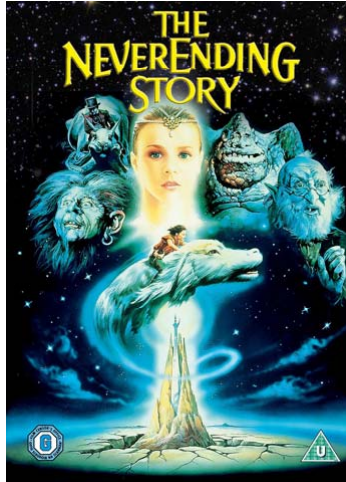
#Miller WG, Myers GL, Gantzer ML, Kahn SE, Schönbrunner ER, Thienpont LM, Bunk DM, Christenson RH, Eckfeldt JH, Lo SF, Nübling CM, Sturgeon CM. Roadmap for Harmonization of clinical laboratory measurement procedures. Clin Chem 2011;57:1108-17.

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Laboratory – Clinician interface

[Non]standardisation and cut-offs

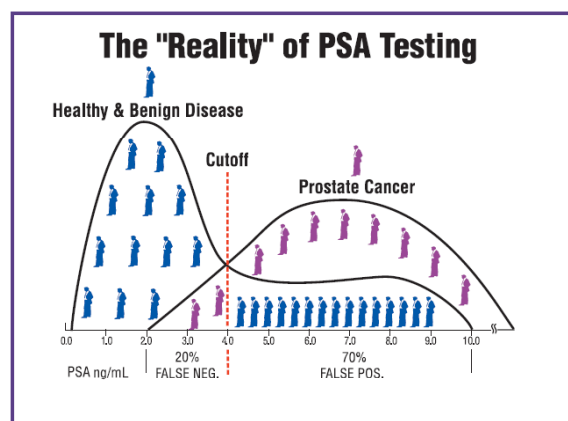


By Dietmar Stöckl
ST Consulting

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tPSA cut-off



Abbott % Free PSA
Physician Monograph

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tPSA cut-off and standardisation

Although most clinicians are familiar with the fact that different tPSA assays produce different results (*#let's just accept that for now*), they may not be aware that restandardization from a historical standard to the WHO calibration causes a shift in mass units, which yields a potential for underestimating tPSA values. **If this shift is not fully appreciated, especially with respect to the tPSA threshold value ("cut-off") for biopsy, a resulting decrease in PCa detection may produce life-altering consequences for individual patients.**

Jansen FH, Roobol M, Bangma CH, van Schaik RHN. Clinical impact of new prostate-specific antigen WHO standardization on biopsy rates and cancer detection. Clin Chem 2008;54:1999-2006.



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tPSA cut-off and standardisation

The finding of a decrease in cancer detection caused by application of the WHO 96/670 calibration (*note: 20% lower than Hybritech*) **may also have positive implications in light of the current discussions on limiting PCa overdiagnosis and subsequent overtreatment.** Because the group of missed cancers contains significantly fewer tumors with a high stage or a high Gleason score and more tumors with favorable characteristics, missing these cancers may not have clinical consequences and so may limit the overdiagnosis and overtreatment of PCa.

Krijg nou wat!

Jansen FH, Roobol M, Bangma CH, van Schaik RHN. Clinical impact of new prostate-specific antigen WHO standardization on biopsy rates and cancer detection. Clin Chem 2008;54:1999-2006.

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Editorial to the Jansen publication



**We suggest an additional possibility,
to abandon the cutpoint of 3 or 4 $\mu\text{g}/\text{L}$ altogether.**

Vickers AJ, Lilja H. Cutpoints in Clinical Chemistry: Time for
Fundamental Reassessment. *Clin Chem* 2009;55:15-7.

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Laboratory – Clinician interface

**We should not throw out the
baby with the bath water!**

Improvement of patient care!

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“Think about”

Eminent scientist

What is the greatest risk factor for prostate cancer?

Visiting your urologist!

Audience laughs ☹️

Morning Tea by Peter Graham



The mole

Unit of amount of substance (mole)

The mole is the **amount of substance** of a system which contains as many elementary entities as there are atoms **in 0.012 kilogram of carbon 12**; its symbol is "mol".

The definition of the mole also determines the value of the universal constant that relates the number of entities to amount of substance for any sample; this constant is called the **Avogadro constant**.

http://www.bipm.org/en/si/si_brochure/

New definition of the kilogram

http://www.redorbit.com/news/science/1983800/new_definition_of_the_kilogram_coming_soon



The kilogram

Current definition

The kilogram is the unit of mass; it is equal to the mass of the international prototype of the kilogram.

Proposed definition

The kilogram, kg, is the unit of mass; its magnitude is set by fixing the numerical value of the **Planck constant** to be equal to exactly 6.62606×10^{-34} when it is expressed in the unit $\text{s}^{-1} \cdot \text{m}^2 \cdot \text{kg}$, which is equal to J·s.

One consequence of this change is that the new definition makes the definition of the kilogram dependent on the definitions of the second and the metre.

New definition of the kilogram

B. Andreas et al. Phys. Rev. Lett. 106, 030801 (2011)
Determination of the Avogadro Constant by
Counting the Atoms in a ^{28}Si Crystal

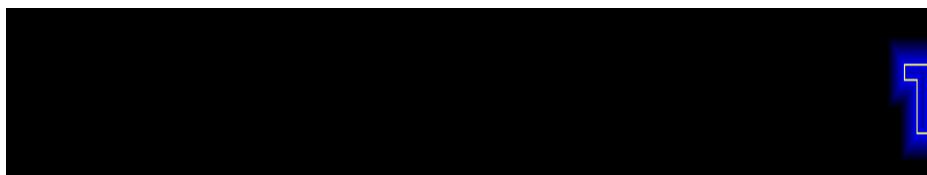
The Avogadro constant links the atomic and the macroscopic properties of matter. Since the molar Planck constant is well known via the measurement of the Rydberg constant, it is also closely related to the Planck constant. The value obtained, is the most accurate input datum for a new definition of the kilogram.

Thanks to the staff of my reference lab



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