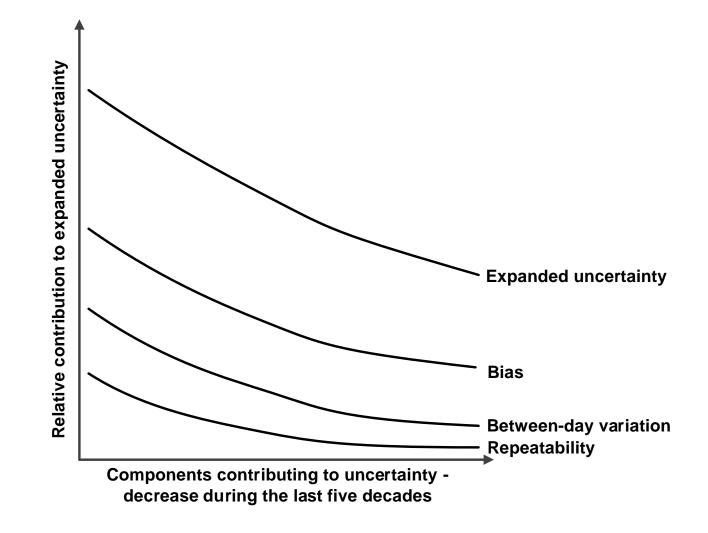
Bias in Clinical Chemistry

Elvar Theodorsson

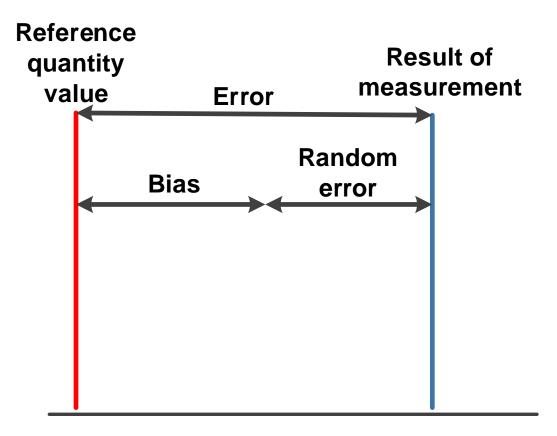


Bias – a major contribution to measurement uncertainty



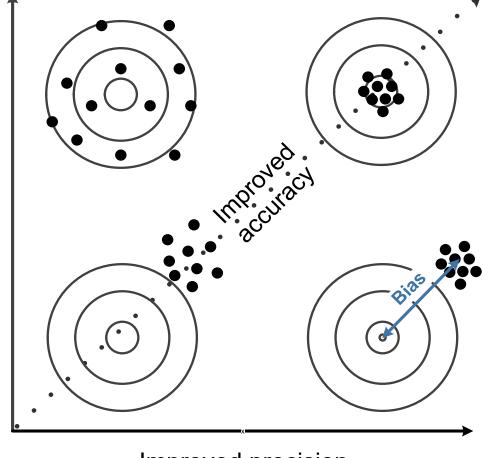


Error components - single measurement result





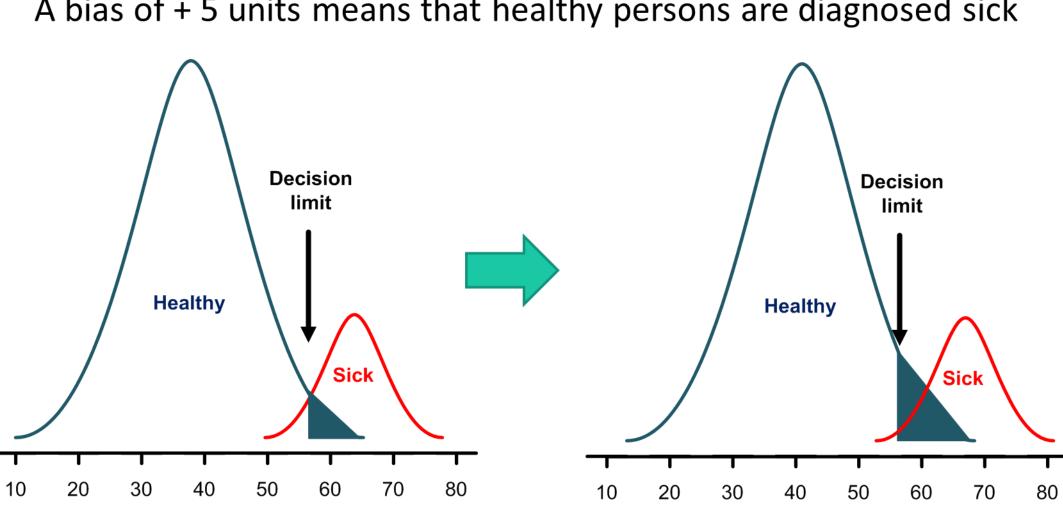
Bias and Imprecision



Improved trueness

Improved precision

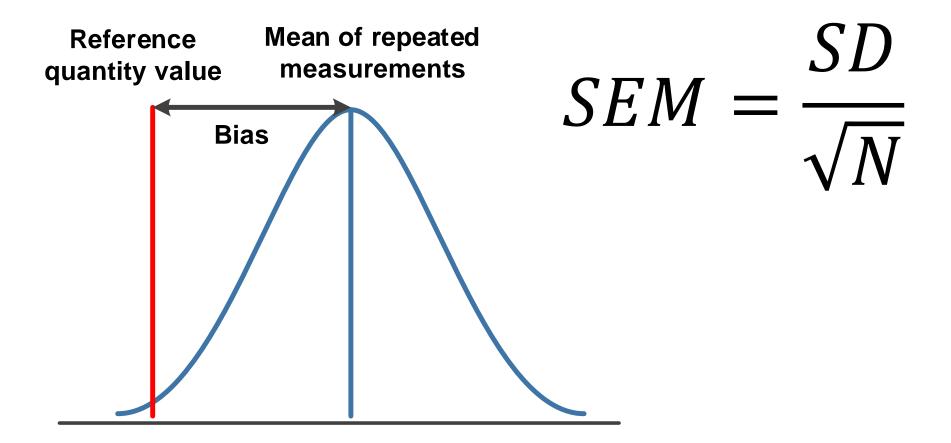




A bias of + 5 units means that healthy persons are diagnosed sick



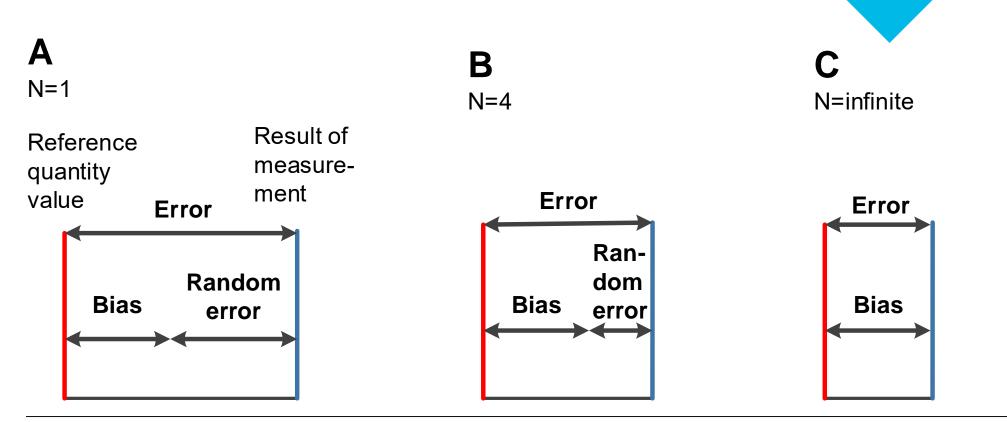
Effect of repeated measurements





Effects of number of replicate measurements

The random error component of the uncertainty in determining the mean is inversely related to the square root of the number of observations – the standard error of the mean (SEM)





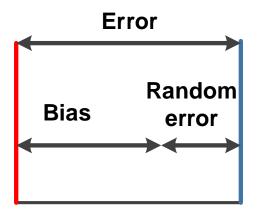
Effects of time

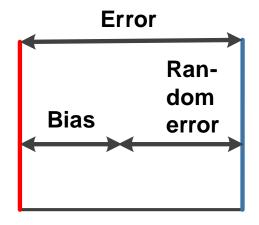
A One day/One run

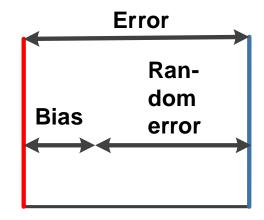
Β

One week/Reagent lot/ Calibration

C One year

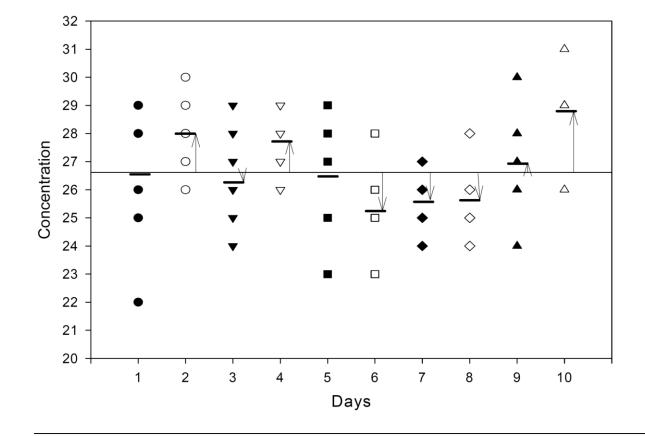








Repeatability - reproducibility





Repeatability - reproducibility

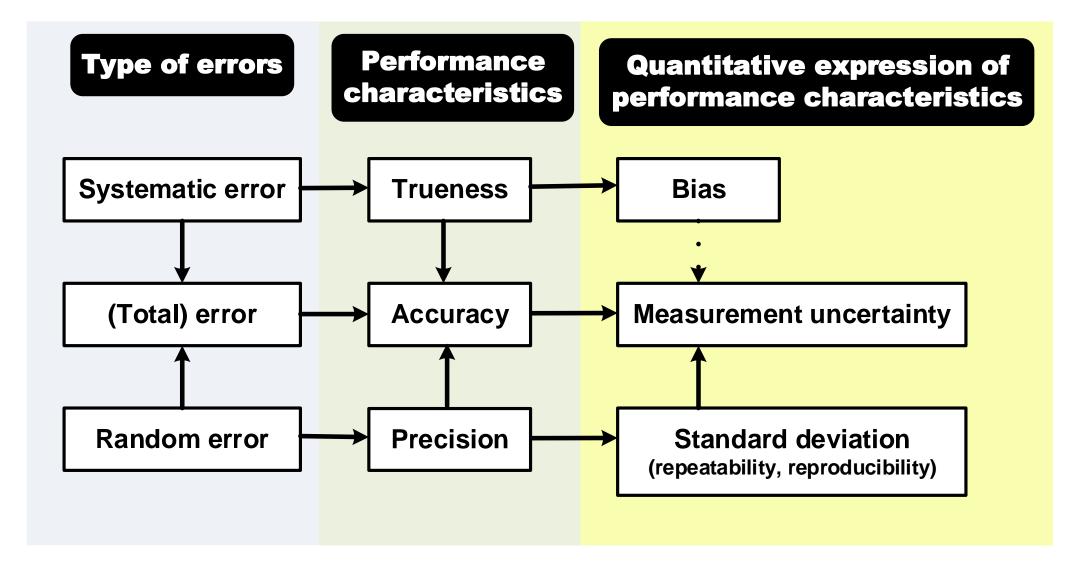
Repeatability

Intermediate reproducibility

Reproducibility

Condition of measurement, out of a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time Condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects







Handling bias

- Eliminate the bias
 - On the national and international level
 - On the local laboratory level
- Include the effects of bias in uncertainty calculations



Eliminating bias on the national and international level

- 1. Standardisation
- 2. Harmonization



The measurand

- The *measurand* "the quantity intended to be measured" is the quantity reflecting the concentration of the chemical constituent you intend to measure in the medically relevant "system" in the patient, e.g. in plasma as a reflection the effects of disease or treatment.
- Is our *intention* to measure the concentration of e.g. glucose in the plasma of the patient or in the patient plasma present in the tube presented to the measurement system?

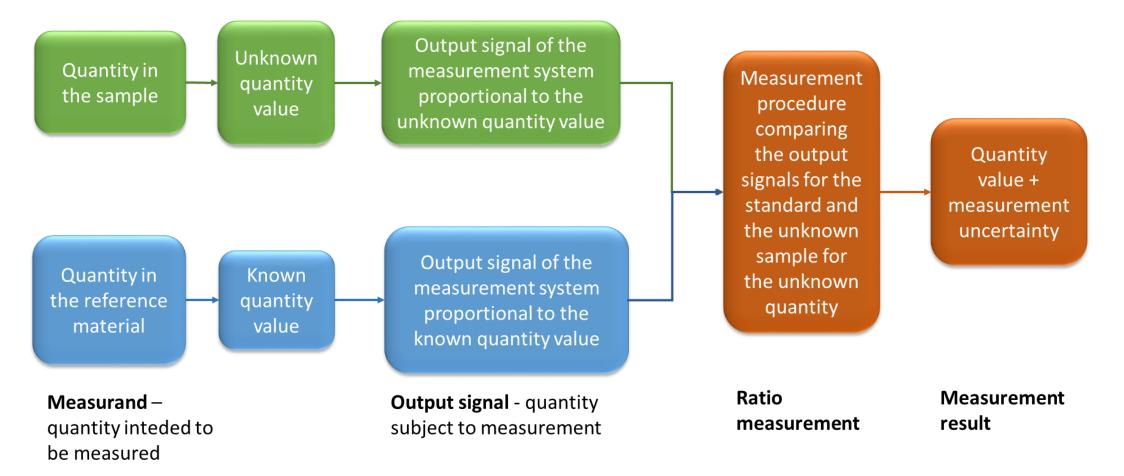


The quantity

- *Quantity* is a generic concept describing the phenomenon (physical signal) being measured. The quantity is not the measurand but its value reflects the concentrations of the measurand.
- A quantity measured in chemistry depends on the chemical structures and chemical reactions that determine its value, but it is ultimately measured by *physical methods*. These physical methods which interact with atoms and molecules measure *quantity values* which visualise and quantify molecular structures or reactions that otherwise would remain invisible.



Measuring means comparing

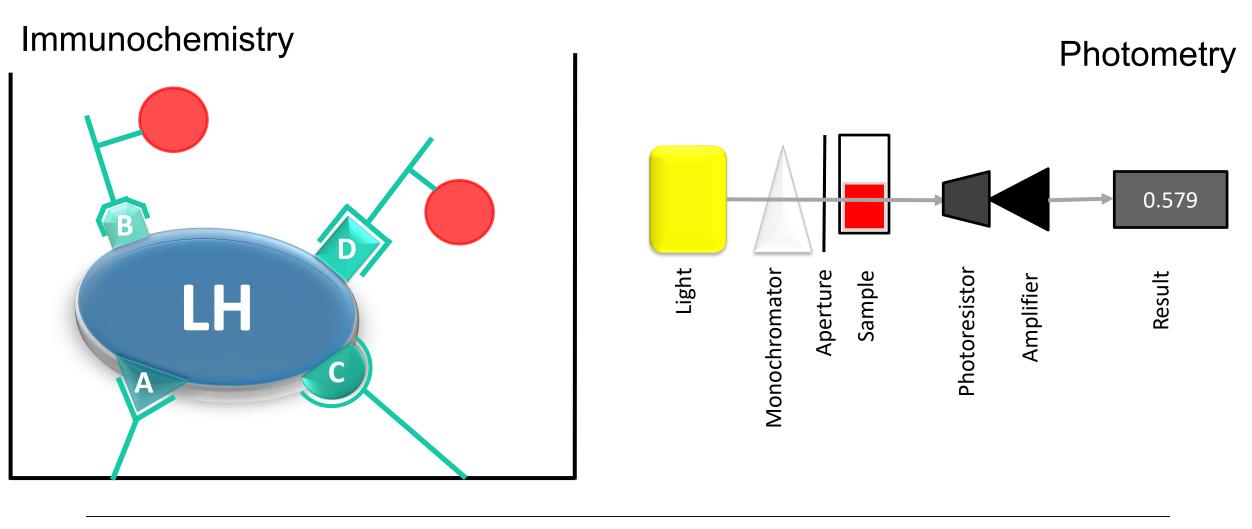




Comparing in chemistry

- Based on physical properties
- Prone to "influence quantities"

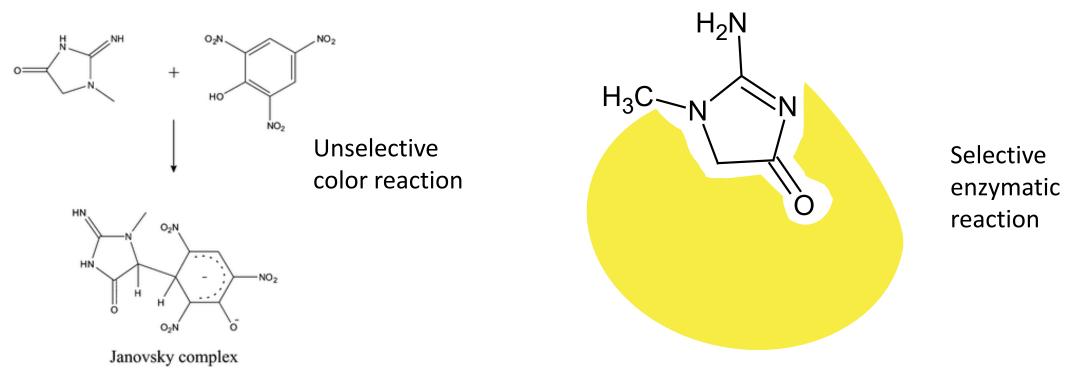


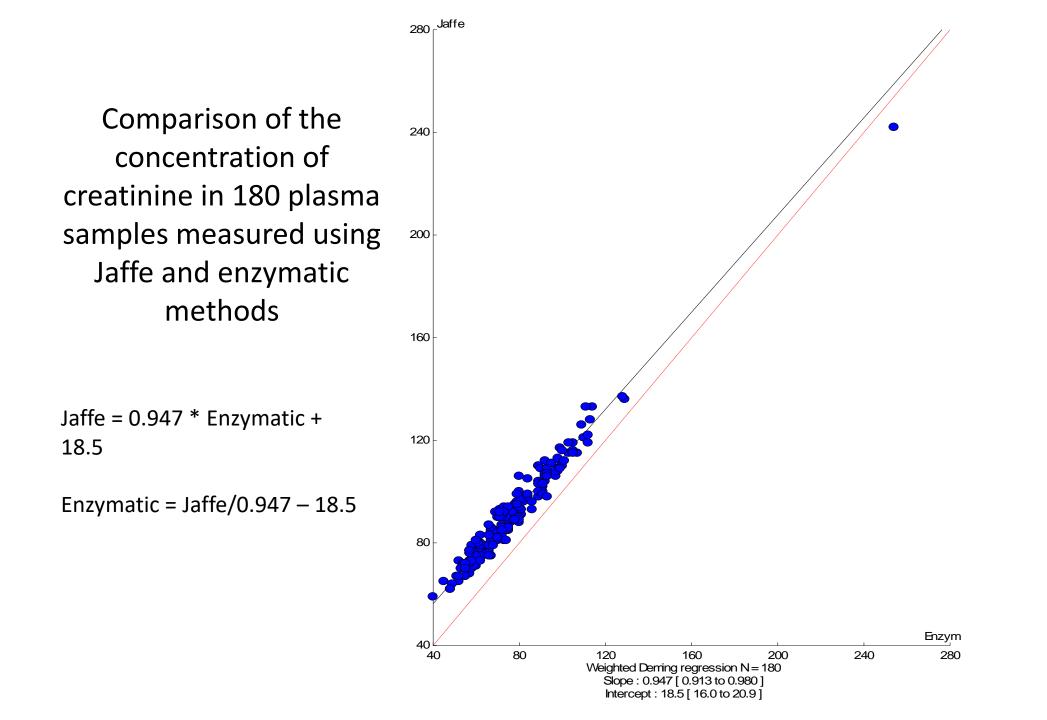




Selectivity VIM 3 - 4.13

"Property of a measuring system used with a measurement procedure, whereby it provides measured quantity value for one or more such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated."



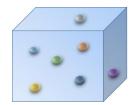


Influence quantities 1(2)

- The presence of "matrix factors"
- Inability to produce the substance in a pure form that can be weighed
- Molecular heterogeneity, e.g. transferrin, LH, FSH, TSH
- Detection of different epitopes







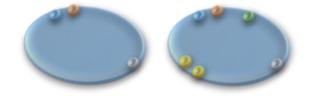




Influence quantities 2(2)

- Lack of knowledge of which epitopes of molecules are medically most relevant, e.g. most substantial biological activity or best diagnostic properties
- Changes in posttranslational modification of molecules e.g. LH and FSH during the ovarial cycle







Matrix effects

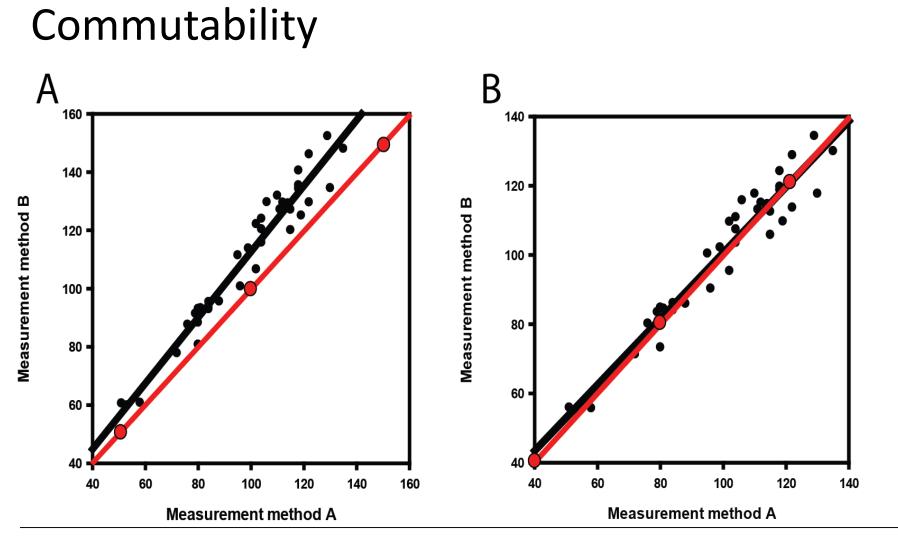
- The combined effect of all components of the sample other than the analyte on the measurement of the measurand.
- If a specific component can be identified as causing a matrix effect then this is referred to as *interference*.



Commutability

- To what extent reference materials, calibrators and control materials show matrix properties similar to those of fresh natural samples.
- Fresh natural patient samples represent the ultimately commutable materials for comparing measurement methods in clinical/biological chemistry.







Commutability of the materials

Material	Primary reference	Secondary reference	Working calibrator	Product calibrator	Patient sample	Detiont
	Commutable?	Commutable?	Commutable?	Commutable?	Commutable!	Patient
Measurement procedure	Primary reference measurement	Secondary reference measurement	Manufacturers measurement		Routine measurement in a clinical laboratory	result
Provider	BIPM, National metrology institutes, accredited reference laboratories	National metrology institutes, accredited reference laboratories	Manufacturers laboratory		End user	
Uncertainty for commutable material Uncertainty for noncommutable material						
Uncertainty for noncommutable material						

Traceability categories (ISO 17511)

	Cate- gory	Reference measure- ment procedure	Primary (pure substance) reference material	Secondary (value assigned) reference material	Examples
ſ	1	YES	YES	POSSIBLE	Electrolytes, glucose, cortisol
Standardization \prec	2	YES	NO	POSSIBLE	Enzymes
	3	YES	NO	NO	Hemostatic factors
Harmonization	4	NO	NO	YES	Proteins, TSH, FSH, LH, tumor markers, HIV
l	5	NO	NO	NO	Proteins, EBV, VZV



Reference materials

Reference material	Usage
Primary Reference Standard	Certified Standard with the highest metrological order. A calibrator with certified purity traceable to the SI unit with associated uncertainty.
Primary Reference Material	Material used for verification of a primary reference method, traceable to the primary reference standard. This material may also be used for verification of a routine method if shown to be commutable.
Secondary Reference Material	Material used for verification of a secondary reference method, traceable to the primary reference standard. This material may also be used for verification of a routine method if shown to be commutable.



Sources of Certified Reference Material and Methods

- JCTLM database (http://www.bipm.org/jctlm/)
 - Reference Materials
 - Reference Measurement Methods
 - Reference Measurement Services





Success stories in standardization in laboratory medicine

- Molecules with simple molecular structures, LC/GC MS, ion-selective electrodes
- Standardization of methods for measuring enzymatic activity
- Enzymatic methods for measuring substances earlier measured by nonspecific colorimetric procedures (e.g. creatinine)
- Cholesterol
- Glycated hemoglobin
- Carbohydrate-deficient transferrin



Harmonization

- Equivalence of measurement results among different routine measurement procedures over time and space according to defined analytical and clinical performance goals
- Any process that enables the establishment of equivalence of reported values produced by different measurement procedures for the same measurand



Standardization and harmonization

- Harmonization encompasses standardization and also addresses those tests that can't be calibrated by traceability to a reference measurement procedure
- Standardization is preferable to harmonization, but it is not always an option even when an internationally accepted calibrator is available. It is preferable due to its traceability to primary reference materials and primary reference measurement procedures

Harmonization has a broader scope than standardization

- Quality systems, e.g. ISO standards
- Concepts, terms, unit of measurement and coding systems
- Preanalytical procedures
 - Patient preparation
 - Specimen collection and handling
- Harmonizing measurement results
- Interpretation of results in medical contexts
- Reference intervals



Comparability and interchangeability of medical laboratory results

- Medical laboratory results should be comparable in time and space across the globe enabling unequivocal diagnosis and monitoring of treatment results
- Multitude of guidelines, standards (ISO), directives (EU IVD directive) and authorities (FDA) govern measurement systems and practices in medical laboratories. These are unfortunately only partially harmonized or unequivocal
 - The EU IVD directive e.g. does not clarify which reference measurement system should be used to fulfil its requirements
 - Organizations at the pinnacle of metrology, lack legal authority



Harmonization strategies 1(2) (Greenberg)

Attribute	Method 1	Method 2
Scheme	Hierarchical standardization per ISO17511:2003. Top down approach passing 'trueness' to lower order measurement procedures and calibrators.	Inter-method comparison as described by International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) (www.harmonization.net). Bottom up approach among routine (commercial) measurement procedures, with no SI traceability.
Reference measurement procedures	One or more higher order reference measurement procedures available , preferably fulfilling requirements of ISO 15193:2009	None available.
Reference materials	Certified purified reference materials and/or commutable secondary reference materials.	No higher order reference materials available. Panel(s) of commutable human samples assigned consensus values through harmonization studies. Some International Conventional Calibrators may be available (e.g. WHO materials), but usually not commutable.



Harmonization strategies 2(2) (Greenberg)

Attribute	Method 1	Method 2
Calibration traceability	Commercial calibrators and reported results for routine measurement procedures traceable to SI unit via a metrological reference system.	Commercial calibrators and reported results of routine measurement procedures not traceable to SI. Traceability linked via inter-method comparison studies of available commercial measurement procedures coupled with mathematical recalibration for removal of systematic differences among reported values.
Sustainability	Inbuilt sustainability through hierarchy of well- characterized and reproducible higher order and lower order reference measurement procedures and reference materials	Risk for non-sustainability of harmonized calibrations over time as routine methods and commercial calibrator lots change. Panels of patient samples used as "calibrators" in harmonization studies to be renewed over time (consumption and/or stability concerns.) Second and subsequent patient sample panels with values traceable to initial sample panel; presumes well-defined specifications for panel member selection.

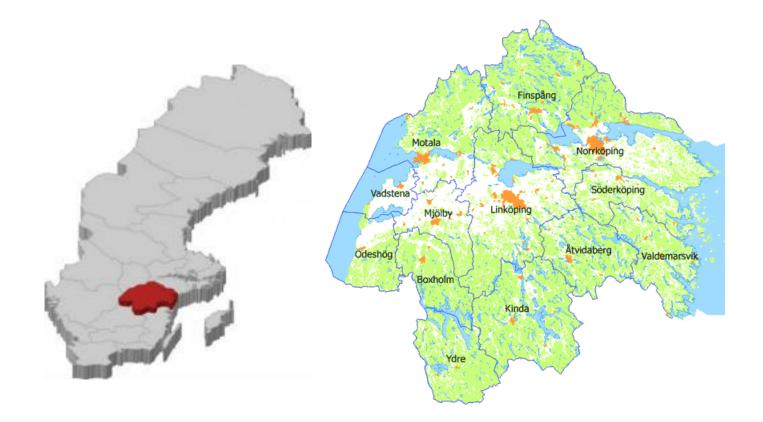


Eliminating bias on the local/laboratory level

- 1. Make sure that there is a shared responsibility for the quality of each measurand in the entire laboratory
- 2. Use the same stabilised control material throughout the entire laboratory
- 3. Use split-sample techniques
- 4. Establish a computer system where all control results are open for everybody within the laboratory to see
- 5. Minimize the number of different measuring procedures and measurement systems
- 6. Use bias and variance component analysis to identify the measurement systems in need of overhaul

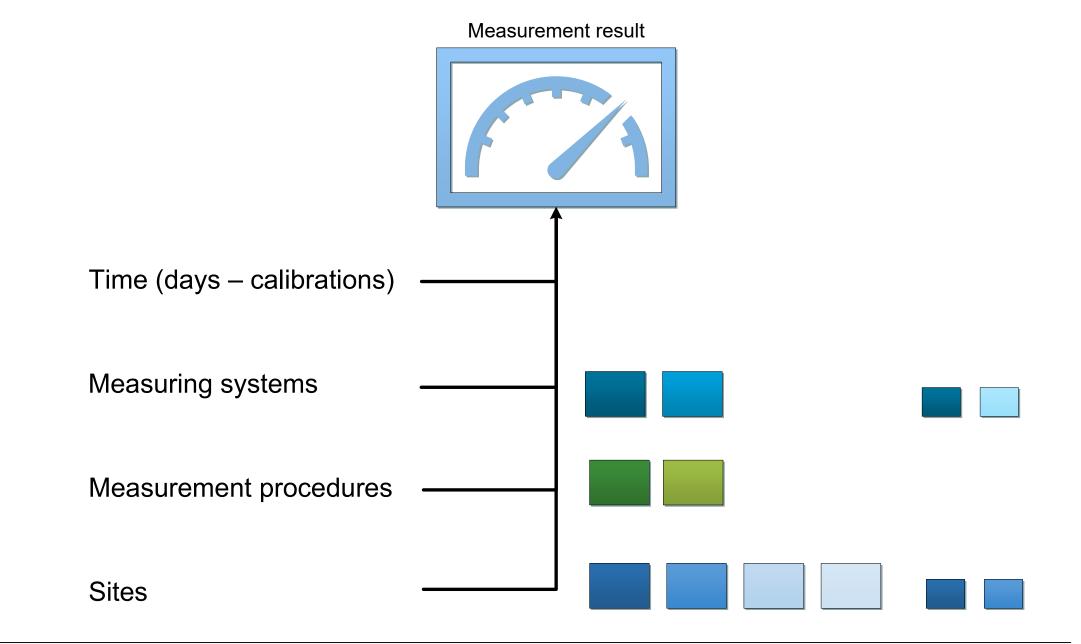


County of Östergötland, Sweden

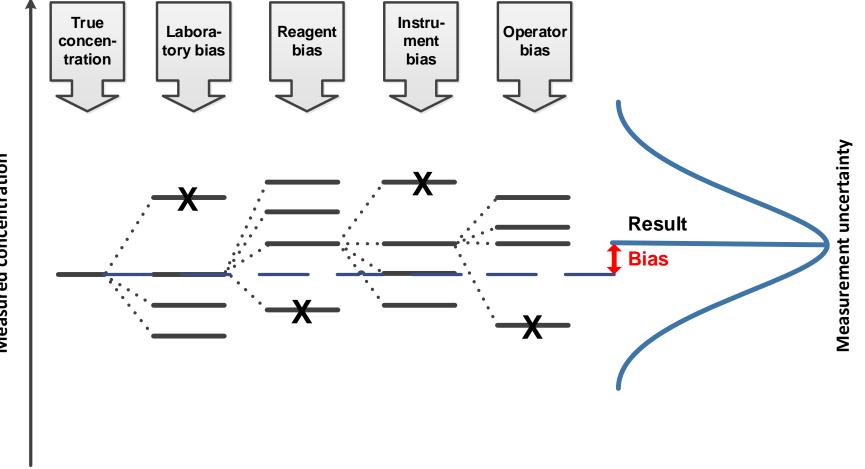


470 000 inhabitants4 hospitals36 primary health care centers









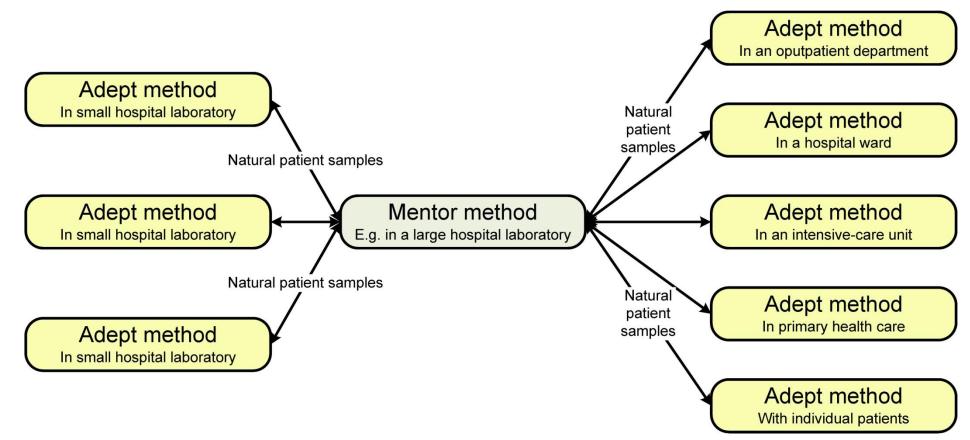
Measured concentration



Split – sample techniques

- 1. Using the same logistic normally used for sending samples to the central laboratory
- 2. Computerize the logistics and evaluation of the data





Split sample/Mentor methods



Norming results

Normed result =
$$\frac{\text{Adept - Mentor}}{\text{Mentor}} *100$$



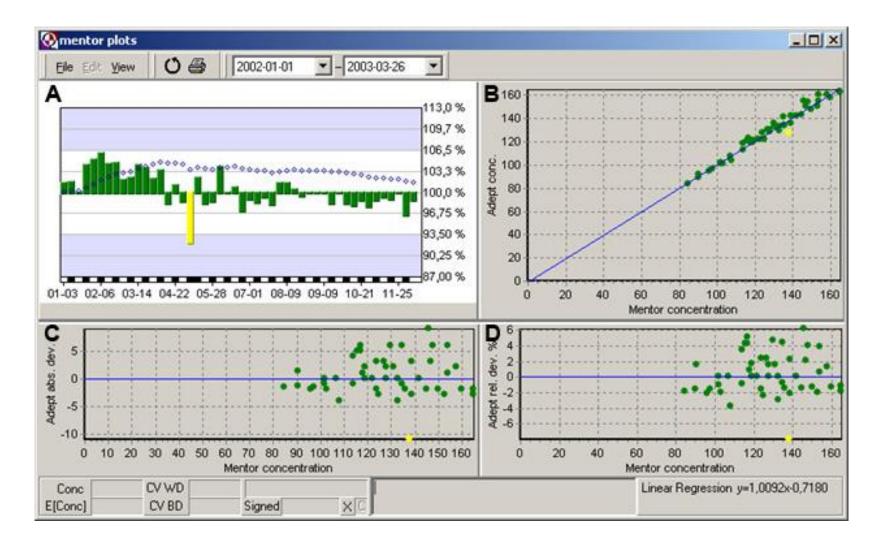
Bias in measurement of endogenous substances

Mtd	:HC Inst	CoID	Mean	CVtotal%	CVtreat%	CVerror%	%CV	n
M1	2454	PPI	336,3	2,658	2,086	1,804	2,325	7
M1	2455	PPI	335,1	3,126	0,7115	3,180	4,963	13
M1	3111	PPI	350,8	4,719	2,319	4,222	4,214	21
M1	3311	PPI	332,5	3,546	2,992	1,946	2,042	2.

Variance component analysis

b/Kemi	Quality Management	Data Analysis	7
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	Analysis, Instrument, ColD		ANP v2.3.13/20100
	2011-05-01 V to V 2011-11-16 V	Separate Sys Mtd Methods D1 Charles ZOV	ANP V2.8.13(20100
	- Accredited	View Control Samples Comp Inst Instruments Median Elsonol ✓ Cytrasts ✓ n	
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		Externa kontroller	
	Sequences Charts		
	and a second	⊞ Strategy M1 3511 PPI 331,6 3,115 1,541 2,817 3,344 14	
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	Aceton - 1802 P Aceton	B 997809-13C-Usea kontroll M1 4011 PPI 334,6 1,906 1,014 1,671 1,968 16	
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	Ab - 1209 P-Albumin	18 33062 - CD23 Lag	
	B Ab/kreaky - Ab/Kreakyot	0 90000 User Tellin M1 4311 PPI 335.2 4.249 2.177 3.777 3.652 16	
	Abakut-Sp - Csv-Abunin	900000 Have Tel bin M1 4411 PPI 340,1 3,159 0,5624 3,218 3,356 16	
	AbEll - P-Albumin, Ellores Abkreaky - Ab/Kreakyot	000004 Fabra Label Cause M1 4612 PPI 328,3 2,208 1,486 1,675 1,673 21	
	Ab/Sp · CsvAbunin	# 999912 - Extern Kontroll, Second Mit 8210 881 226.0 1.626 1.061 1.128 1.897 20	
	Aldo 1703 S-Aldosteron	B 999999 - Patientkontroll LMC M1 6211 PPI 338.8 2.666 1789 2.049 2.127 24	
	ALP · 1214 P-Fostatas, akalisi	Bioinmun Immunoassay, progr M1 6212 PPI 329,7 3,107 0,5736 3,142 3,403 19	
	⊕ Amylas - 1219 Amylas	Cataken1 - Lakemedel M1 6213 PPI 336,8 2,251 0,6895 2,223 3,089 15 Cataken2 - Lakemedel M1 6214 PPI 344,8 3,663 2,347 2,629 3,357 20	
	AntiFXa - 1410 P-AntiTaktor Xi	E Calilkem2-Likkenedel M1 6214 PPI 344,8 3,693 2,347 2,929 3,357 20 Calilkem3-Likkenedel M1 6215 PPI 342,1 2,134 1,337 1,701 2,741 24	
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	Asat - 1215 P-Asat		
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	 BilD - 1213 P-Bilirubin, konjugi bM2 - Anti-M2 (IgG) 	e ozalio loheno M1 3111 PPI 90,13 5,542 4,323 3,552 3,491 20	
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	CDT · S-CD-transferrin	(e equinetho - MMA + Homocyste M1 4111 PPI 91,36 13,70 13,64 1,304 1,531 14	
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	CK • 1220 P+OK, total:	INSTAKDA2-Koogulation, spz M1 4411 PPI 90,41 3,279 3,143 0,8895 1,047 16 Lipikom1-Libkenedel M1 4512 PPI 86,35 10,40 10,37 0,7372 0,7335 21	
	CI - P-Klorid	B Ldskem1-Låkernodel M1 4612 PPI 88,35 10,40 10,37 0,7372 0,7335 21 B Ldskem2-Låkernodel M1 5202 PPI 90,86 5,596 5,513 0,9712 0,9794 53	
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	CHOV - BV-Klond EVClond CHOVALOND CHOVA - BV-Klond	B UKD0W/N1 Downs screening M1 6212 PPI 90,69 4,476 4,400 0,8445 0,9532 19	
	 EFUB - 3203 Nono Folaysat EFuB - v6-Klovid 	B UKDDW/N2 - Downs screening M1 6213 PPI 87,98 5,980 5,929 0,8109 0,9456 15	
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Advantages of split samples

- 1. The the material has optimal matrix properties (is commutable)
- 2. The material is available without cost for all laboratories accepting routine patient samples
- 3. There is general agreement that all measurement systems and reagents should optimally result in identical results when analyzing the same patient samples
- 4. The methods are optimal for identifying the measurement system(s) in the organization that contribute the largest part of the overall measurement uncertainty due to bias. Split sample methods are laborious in the absence of effective computerized systems, but convenient when properly implemented

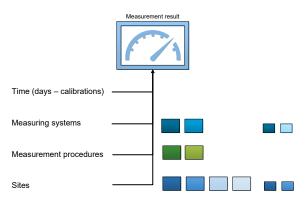


Bias elimination at the laboratory level – practical laboratory work



Shared responsibility for the quality of each measurand in the entire laboratory

- A sample from a certain patient can encounter all factors causing variation of results in the laboratory
- The overall measurement uncertainty therefore needs to be an issue and shared responsibility for the entire organization
- In time this caters for a better working environment in the entire organization





Use the same stabilised control material throughout the entire laboratory

- 1. Test materials from different producers for optimal matrix properties in the situation you have in your own laboratory
- 2. Materials of human plasma/serum origin are most likely to show optimal matrix properties
- 3. Purchase a supply of the control material lasting at least one year preferably two years



Establish a computer system where all control results are open for everybody within the laboratory to see

- Appropriate computerized system is a prerequisite to be able to shoulder shared responsibility for the measurement uncertainty of each measurand in the laboratory
- Both graphical and statistical presentation



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9 - Iohexol nivå 1	8311 PPI	2454 PPI	n EVF [1107 B-Erytrocyter, volymfraktion 2455 PPI	3111 PPI	3311 PPI	3411 PPI	3511 PPI	3611 PPI	3711 PPI	3811 PPI	3911 PPI
7 - Iohexol, nivå 2 8 - MMA, nivå 1	وروب و و و کار د د و و د در و		بور الموسور ومورو مسرور السم	ہے این اس اس سے 🗹 انتاز اس ہے اس اس اس این	ور او	المتوام اعتلم اعتلم اعتلم المترام المترام المراب الم	ودددوه وددواوه الدنوي ودوي			ana a a a a a a a a a a a a a a a a a a	روندن و الالدندين ورندو بدن الاند
9 - 13C-Urea kontroll									and anone fillinger	aller a series	
4 · CD 29 Hög	EVF [1107 B-Erytrocyter, volymfraktion	n EVF [1107 B-Erytrocyter, volymfraktio	n EVF [1107 B-Erytrocyter, volymfraktion 408 PPI	EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfraktion		EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfr
2 - CD29 Låg			1 ** 1		-						
0 - CD29 Normal 8 - HemoTrol, låg	و دو و سه دو و و و ه ک و و		R-Reserved <mark>I</mark> n-afted <mark>I</mark> ne IIalial	~ ₽ ₽₽₽₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩	alastinatiologistististess	▋ <mark>」</mark> ≈₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩₩	and Relations	**************************************	watel a grant all the sector is a		⊐∼ <mark>⋳</mark> ⋛⊐∼⋍⋳⋳⋍⋳⋳⋍⋍⋳
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4 - Extern kontroll,Seronc	6213 PPI	6214 PPI	n EVF [1107 B-Erytrocyter, volymfraktion 6215 PPI	6216 PPI	6217 PPI	EVF [1107 B-Erytrocyter, volymfraktion 6218 PPI	6219 PPI	7108 PPI	8011 PPI	EVF [1107 B-Erytrocyter, volymfraktion 8211 PPI	8311 PPI
2 - Extern kontroll,Seron			اس اید اور								
99 - Patientkontroll, LMC											
un - Immunoassay, progi em1 - Läkemedel	EVF [1107 B-Erytrocyter, volymfraktion 8511 PPI	n EVF [1107 B-Erytrocyter, volymfraktio 8611 PPI	n EVF [1107 B-Erytrocyter, volymfraktion 8711 PPI	EVF [1107 B-Erytrocyter, volymfraktion 8311 PPI	xFe[1240 P-Järn] 7205 PPI	xFe[1240 P-Jörn] 7206 PPI	Fib [P-Fibrinogen] 330 PPI	Fib [P-Fibrinogen] 331 PPI	GGT [1224 P-Y-Glutamyltransferas] 223 PPI	GGT [1224 P-Y-Glutamyltransferas] 2500 PPI	GGT [1224 P-Y-Glutamyltransfer 254 PPI
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em3 - Läkemedel							1997 1997 1997 1997 1997				
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onf - Koagulation ba - Koagulation	GGT [1224 P-Y-Glutamyltransferas] 3703 PPI	GGT [1224 P-Y-Glutamyltransferas] 3803 PPI	GGT [1224 P-Y-Glutamyltransferas] 4403 PPI	GGT [1224 P-Y-Glutamyltransferas] 6600 PPI	GGT [1224 P-Y-Glutamyltransferas] 6601 PPI	GGT [1224 P-Y-Glutamyltransferas] 6605 PPI	GGT [1224 P-Y-Glutamyltransferas] 6606 PPI	GGT [1224 P-Y-Glutamyltransferas] 6607 PPI	GGT [1224 P-Y-Glutamyltransferas] 6608 PPI	GGT [1224 P-Y-Glutamyltransferas] 6603 PPI	GGT [1224 P-Y-Glutamyltransfer 7205 PPI
x · Koagulation	·	ast i <mark>- 11</mark> -su-									
reen - Koagulation											
on - Blodgaser	GGT [1224 P-Y-Glutamyltransferas] 7206 PPI	GGT [1224 P-Y-Glutamyltransferas] 8603 PPI	fGluk [1233 fP-Glukos(fastande)] 2500 PPI	PGluk [1233 P-Glukos (fastande)] 254 PPI	PGluk [1233 P-Glukos (fastande)] 7205 PPI	PGluk [1233 P-Glukos (fastande)] 7206 PPI	Gluk-vB [vB-Glukos] 8903 PPI	Gluk-vB (vB-Glukos) 8905 PPI	xxHb [aB-Hemoglobin] 4431 PPI	xxHb [aB-Hemoglobin] 4688 PPI	Hb [1108 B-Hb(Hemoglobin)] 2454 PPI
ndo1 - Endokrinologi ndo2 - Endokrinologi	-										
lk · Alkoholer		Rangelighen <mark>- Radio -</mark> R	anda <mark>```a`a`aaaaaaaaaaaaaaaaaaaaaaaaaaaa</mark>	~~ <u>₽</u> ~₽₽₽₽~₽ [₽] ₽₽₽~	a-a <mark>n</mark> a-a <u>y</u> aaan		and a state of the second		~~ <u>~~</u> ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~		ایر ساری سا سال سال
dt - CD-Transferrin	Hb [1108 B-Hb(Hemoglobin)] 2455 PPI	Hb [1108 B-Hb(Hemoglobin)] 3111 PPI	Hb [1108 B-Hb(Hemoglobin)] 3311 PPI	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)] 3511 PPI	Hb [1108 B-Hb(Hemoglobin)] 3611 PPI	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)] 3811 PPI	Hb [1108 B-Hb(Hemoglobin)] 3311 PPI	Hb [1108 B-Hb(Hemoglobin)] 4011 PPI	Hb [1108 B-Hb(Hemoglobin)] 407 PPI
sv - Proteinanalyser i spi	2455 PPI	3111 PPI	3311 PPI	Hb [1108 B-Hb(Hemoglobin)] 3411 PPI	3511 PPI	3611 PPI	Hb [1108 B-Hb(Hemoglobin)] 3711 PPI	38f1 PPI	3911 PPI	4011 PPI	407 PPI
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ores3 · Elfores											
em4000 - Hematologi	Hb [1108 B-Hb(Hemoglobin)] 408 PPI	Hb [1108 B-Hb(Hemoglobin)] 4111 PPI	Hb [1108 B-Hb(Hemoglobin)] 415 PPI	Hb [1108 B-Hb(Hemoglobin)] 4311 PPI	Hb [1108 B-Hb(Hemoglobin)] 4411 PPI	Hb [1108 B-Hb(Hemoglobin)] 4612 PPI	Hb [1108 B-Hb(Hemoglobin)] 5202 PPI	Hb [1108 B-Hb(Hemoglobin)] 6210 PPI	Hb [1108 B-Hb(Hemoglobin)] 6211 PPI	Hb [1108 B-Hb(Hemoglobin)] 6212 PPI	Hb [1108 B-Hb(Hemoglobin)] 6213 PPI
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oaB - Koagulation	6214 PPI	6215 PPI	6216 PPI	6217 PPI	6218 PPI	6219 PPI			8011 PPI	8211 PPI	8311 PPI
p1 - Lipoprotein											
p2 - Lipoprotein nia - Albumin i urin, låg ni									-		
rot - P-protein	Hb [1108 B-Hb(Hemoglobin)] 8511 PPI	Hb [1108 B-Hb(Hemoglobin)] 8611 PPI	Hb [1108 B-Hb(Hemoglobin)] 8711 PPI	Hb [1108 B-Hb(Hemoglobin)] 8911 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 2404 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 3570 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 3670 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 3770 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 3870 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 3975 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S) 4170 PPI
et - Retikulocyter											
pr - U-Protein											
tho - MMA + Homocyste KOA1 - Koagulation, spε	xÖHbA1c [Hb(B)·HbA1c (Mono S)] 4370 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 4470 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 6382 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 6383 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 6385 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 6386 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 6388 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 8070 PPI	xÖHbA1c [Hb(B)·HbA1c (Mono S)] 8170 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 8270 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S 8370 PPI
KOA2 - Koagulation, spe	4310 PPI		0302 PPI	6303 PPI	0305 PPI	0300 PPI	0300 PPI	6010 PPI			6310 PPI
m1 · Läkemedel											
m2 - Läkemedel	OUL MATTER (D) IN 14 (D) CO			-046 445 746 785 18 14 781 - 273					HDI KALTOOS DUDI KALAN D		
fentorkontroll	xÖHbA1c [Hb(B)·HbA1c (Mono S)] 8570 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 8670 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono \$)] 8770 PPI	xÖHbA1c [Hb(B)-HbA1c (Mono S)] 8870 PPI	xÖHbA1c [Hb(B)·HbA1c (Mono S)] 8970 PPI	pHbA1cIF [B-HbA1c (IFCC) pv] 2652 PPI	pHbA1cIF [B-HbA1c (IFCC) pv] 6380 PPI	pHbA1clF [B-HbA1c (IFCC) pv] 8470 PPI	xHDLKol [1228 P-HDL-Kolesterol] 2500 PPI	xHDLKol [1228 P-HDL-Kolesterol] 254 PPI	xHDLKol [1228 P-HDL-Kolestero 3803 PPI
WN1 - Downs screening											
WN2 · Downs screening											
WN3 - Downs screening	xHDLKol [1228 P-HDL-Kolesterol] 4403 PPI	xHDLKol [1228 P-HDL-Kolesterol] 6600 PPI	xHDLKol [1228 P-HDL-Kolesterol] 6601 PPI	xHDLKol [1228 P-HDL-Kolesterol] 6605 PPI	xHDLKol [1228 P-HDL-Kolesterol] 6606 PPI	xHDLKol [1228 P-HDL-Kolesterol] 6607 PPI	xHDLKol [1228 P-HDL-Kolesterol] 6608 PPI	xHDLKol [1228 P-HDL-Kolesterol] 6603 PPI	xHDLKol [1228 P-HDL-Kolesterol] 7205 PPI	xHDLKol [1228 P-HDL-Kolesterol] 7206 PPI	xHDLKol [1228 P-HDL-Kolesterol 8603 PPI
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Results panel

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2000-01-01 - 2001-08-11 -	KL\Klinisk ke	mi∖KS Klin k	emi (KSKK) 🖌	LUSTIX20, UGlukos (remsa)				
Use NPU components	N Lid	Method	Mean	CV	CV C	Ň	FirstDay	LastDay
Use LID translation	9999680	2093	2,116	26,6	26,6	95	2001-01-10	2001-06-07
Group by methods								
Accredited series only	KL\Klinisk ker	mi∖KS Klin k	emi (KSKK) : (GT20, S0	ST			
Separate subgroups	N Lid	Method	Mean	CV	CV C	N	FirstDay	LastDay
. <u></u>	9999110	2002	1,162	2,96	2,96	572	2001-01-10	2001-06-08
Klinisk Immunologi	9999130	2002	5,442	8,75	8,75	155	2001-01-10	
- Klinisk farmakologi	9999160	2001	1,165	5,17	5,17	392	2001-01-10	
	9999170	2001	5,622	6,88	6,88	137	2001-01-10	
⊡ Klinisk kemi ⇔ DC Klinikerni (DCKK)	9999180	2003	1,180	3,01	3,01	267		2001-06-07
🗈 DS Klin kemi (DSKK)	9999180	2007	1,200			1	2001-05-01	
Extern Verksamhet	9999184	2007	1,167	2,77	2,77	181		2001-06-08
⊞ KS Klin kemi (KSKK)	9999190	2003	5,489	6,55	6,55	111	2001-01-10	
⊞ KS Klin kemi spec (KSS		2007	5,450			1	2001-05-01	2001-05-01
⊡ NS Klin kemi (NSKK)	9999194	2007	5,636	7,64	7,64	101	2001-01-10	2001-06-08
····· All results	I							
			emi (KSKK) : I			. .		
	N Lid	Method	Mean	CV	CV C	N	FirstDay	LastDay
	9999701	2146	0,7763	3,45	3,45	3	2001-05-31	2001-06-07
	9999701	2147	0,8409	3,31	3,31	94	2001-01-10	
	9999702	2146	1,593	3,83	3,83	3	2001-05-31	2001-06-07
	9999702	2147	1,681	2,42	2,42	91	2001-01-10	2001-06-07
	Lesser - L	SKC KP I						
	N Lid	Method	emi (KSKK) : H Mean	16, Бнеі CV	moglopin CV C	(mass) N	FirstDay	LastDay
	9999100	2014	59,59	5,07	5,07	367	2001-01-10	
	9999100	2015	58,85	2,06	2,06	240		2001-06-07
	9999100	2015	58,52	2,00	2,00	389		2001-06-08
	9999400	2010	119,6	1,88	1,88	389	2001-01-10	
	9999400	2015	120,4	1,78	1,78	245	2001-01-10	
	9999400	2016	118,0	1,98	1,98	410		2001-06-08
	9999500	2014	59,70	1,53	1,53	27	2001-02-23	
	9999500	2014	59,00	1,23	1,23	20	2001-02-23	
	9999500	2016	58,82	1,54	1,54	28	2001-02-23	
	9999600	2014	120,3	0,930	0,930	30	2001-02-23	
	9999600	2015	120,9	0,802	0,802	19	2001-02-23	2001-04-23
	9999600	2016	119,3	1,42	1,42	31		2001-04-24
		2010					200.02.20	200. 04 24
	KI \Klinisk ker	mi∖KS Klin k	emi (KSKK) : I	HCG24 EI	X00366			
	N Lid	Method	Mean	CV	CV C	N	FirstDay	LastDay
	9999370	2006	2,840	· ·		1	2001-04-30	2001-04-30
	9999380	2004	4,580	37,2	37,2	218	2001-01-09	2001-04-00
	9999380	2004	5,145	30,2	30,2	191	2001-01-03	2001-06-08
	9999390	2004	24,42	8,16	8,16	228	2001-01-09	2001-06-07
		2001	21,12	0,10	0,10	220	2001 01 00	2001 00 01
	1							

Structure tree

Minimize the number of different measuring procedures and measurement systems

- Must be done over an extended period of time for economic reasons
- Make lot-number variability amongst the important criteria when selecting a supplier



Change LOT-numbers simultaneously throughout the entire laboratory

- Purchase large amounts of the same LOT-numbers in order to minimize the number of LOT-number changes/recalibrations
- Receive reagents centrally and use your distribution network to distribute reagents, calibrators and controls



"If it ain't broke, don't fix it"

- Frequent lot-number changes/recalibrations are a common cause of uncertainty
- Identify the most important sources of variation and eliminate them



Use bias- and variance component analysis to identify the measurement systems in need of overhaul

- Create automated computer solutions for the purpose
- Simple solutions including MS Excel spreadsheets will in time prove insufficient for large laboratories



Calculating with bias

- 1. Identify and eliminate causes of imprecision and bias
- 2. Calculate uncertainty

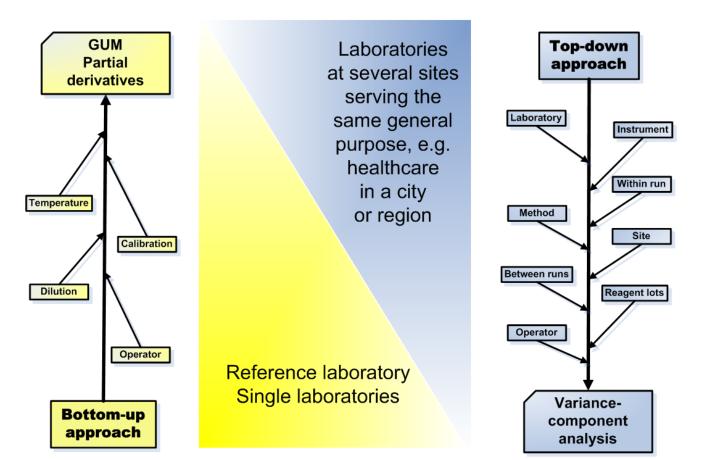


Law of propagation of error

- Calculus for combining uncertainties from multiple variables to estimate uncertainty
 - Simple addition of variances of the various variance components
- Partial derivatives, Taylor series etc.
 - Appropriate for measurement equations



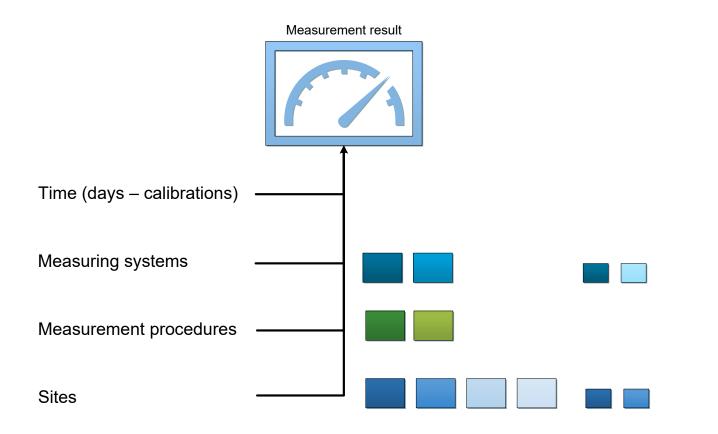
Top down vs Bottom up measurement uncertainty



С

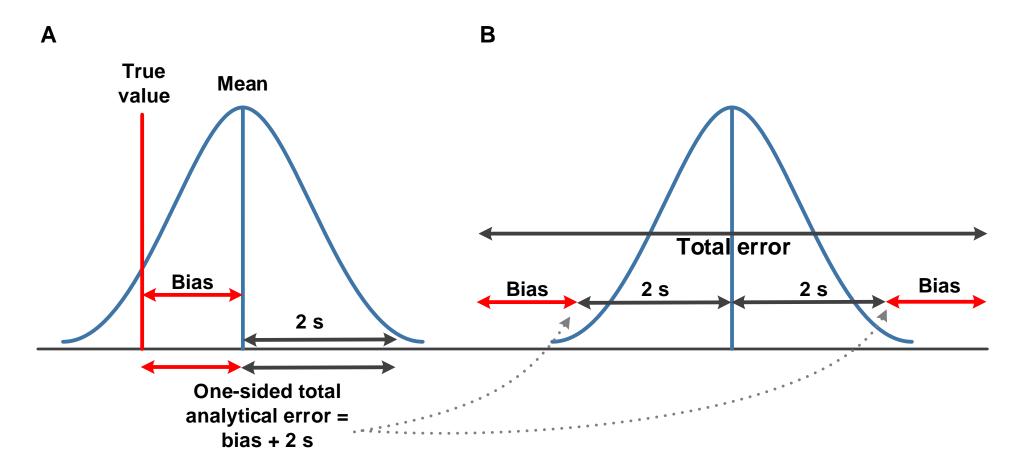


Main factors causing variation in results



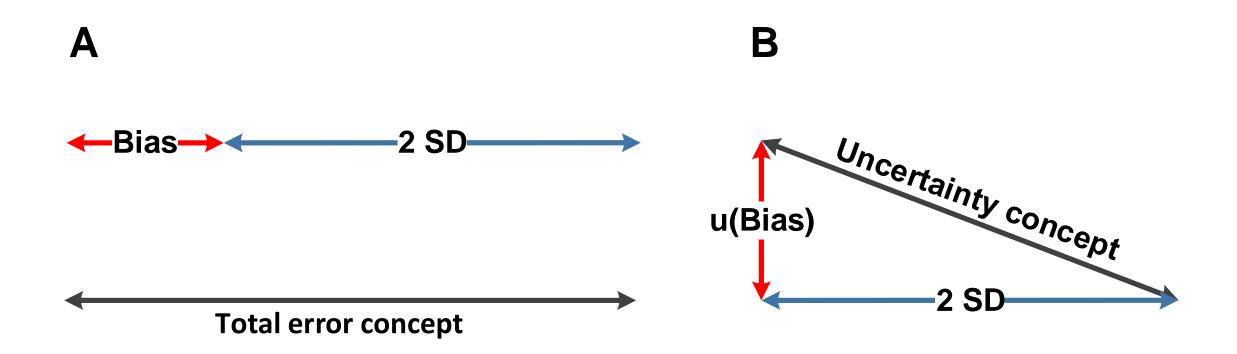


Westgard – single and double sided





Adding uncertainties





RiliBÄK- approach (Richtlinien der Bundesärztekammer)

$$\Delta_{max} = \sqrt{k^2 * s^2 + Bias^2}$$

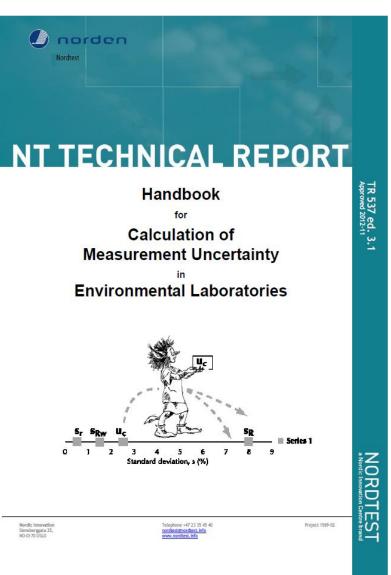
- Δ_{max} =Maximum allowable error when measuring a control sample
- s = standard deviation
- k = a statistical coverage factor which depends on the purpose
- Bias = mean concentration measured in the control samples target value of the control sample provided by its manufacturer



The TROLL book

Handbook for Calculation of Measurement Uncertainty in Environmental Laboratories

<u>http://www.nordtest.info/index.php/tec</u> <u>hnical-reports/item/handbook-for-</u> <u>calculation-of-measurement-uncertainty-</u> <u>in-environmental-laboratories-nt-tr-537-</u> <u>edition-3.html</u>



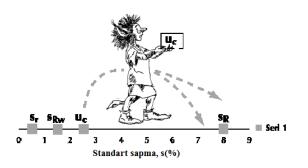


The TROLL book

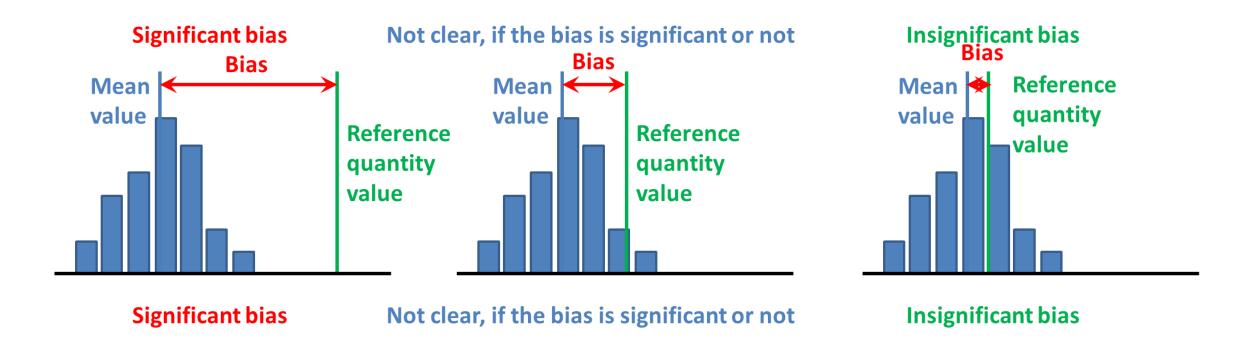
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<u>http://www.nordtest.info/images/doc</u> <u>uments/nt-technical-</u> <u>reports/NT_TR_537_edition4_Trk.pdf</u> NORDTEST NT TR 537 edition 4 Türk 2019:02

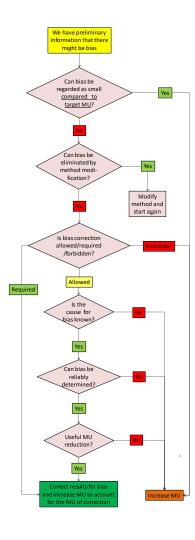
Çevre Laboratuvarlarında Ölçüm Belirsizliği Hesaplamaları için El Kitabı











There is no point in trying to eliminate or correct small bias, since both elimination and

correction need resources. However it should be

possible, is to try to eliminate it by modifying th

either impossible or impractical then we ca

consider correcting for bias. There are thre

. Correction may be required. If so, we have

. Correction can be forbidden. If so, then w

into account as an uncertainty source.

correction is justified.

include bias into the MU estimate

would have been without correction.

included in uncertainty

without correction

cannot correct and we have to take the bia

Correction may be allowed. Then we will loo at three more criteria to determine wheth

is not recommended and it is more reasonable

Why so? This is because if the cause of bias is no

known then in our future results the bias may be

absent and if we then correct then we make ou

result more wrong than it would have bee

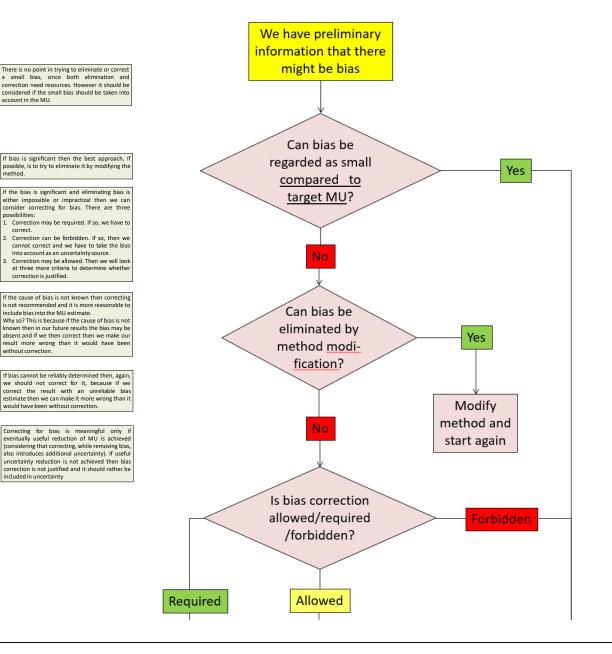
Correcting for bias is meaningful only

account in the MU

method.

nossihilities

correct



There is no point in trying to eliminate or correct a small bias, since both elimination and correction need resources. However it should be \diamond considered if the small bias should be taken into account in the MU.

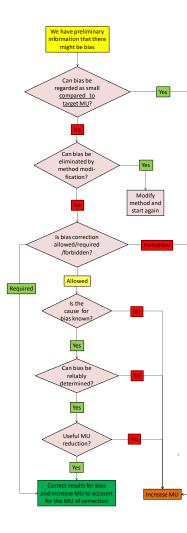
¢

If bias is significant then the best approach, if possible, is to try to eliminate it by modifying the method.

If the bias is significant and eliminating bias is either impossible or impractical then we can consider correcting for bias. There are three possibilities:

- 1. Correction may be required. If so, we have to correct.
- 2. Correction can be forbidden. If so, then we cannot correct and we have to take the bias into account as an uncertainty source.
- 3. Correction may be allowed. Then we will look at three more criteria to determine whether correction is justified.





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include bias into the MU estimate

without correction

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If the cause of bias is not known then correcting is not recommended and it is more reasonable to

Why so? This is because if the cause of bias is no

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If bias cannot be reliably determined then, again,

we should not correct for it, because if we

correct the result with an unreliable bias estimate then we can make it more wrong than it

Correcting for bias is meaningful only

eventually useful reduction of MU is achieved

(considering that correcting, while removing bias

also introduces additional uncertainty). If useful

uncertainty reduction is not achieved then bias correction is not justified and it should rather be

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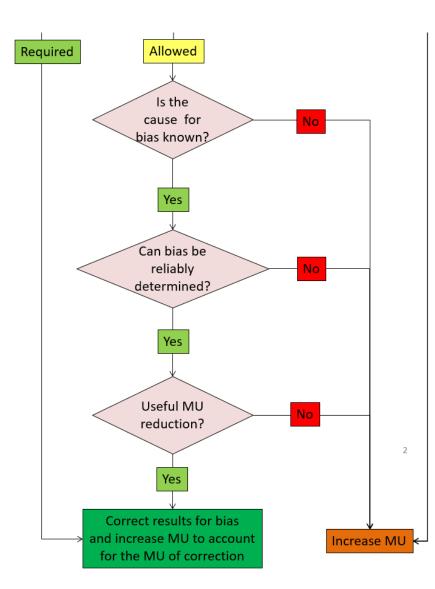
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nossihilities

correct



If the cause of bias is not known then correcting is not recommended and it is more reasonable to include bias into the MU estimate. Why so? This is because if the cause of bias is not known then in our future results the bias may be absent and if we then correct then we make our result more wrong than it would have been without correction.

If bias cannot be reliably determined then, again, we should not correct for it, because if we correct the result with an unreliable bias estimate then we can make it more wrong than it would have been without correction.

Correcting for bias is meaningful only if eventually useful reduction of MU is achieved (considering that correcting, while removing bias, also introduces additional uncertainty). If useful uncertainty reduction is not achieved then bias correction is not justified and it should rather be included in uncertainty



Relative standard uncertainty

- The standard deviation divided by the mean
- %CV is that figure expressed as percent

100	-0.5	0.25	1000	-5	25
101	0.5	0.25	1010	5	25
100	-0.5	0.25	1000	-5	25
99	-1.5	2.25	990	-15	225
101	0.5	0.25	1010	5	25
102	1.5	2.25	1020	15	225
99	-1.5	2.25	990	-15	225
100	-0.5	0.25	1000	-5	25
101	0.5	0.25	1010	5	25
102	1.5	2.25	1020	15	225
100.50	Mean		1005.00	Mean	
1.08	SD		10.80	SD	
1.07	%CV		1.07	%CV	
0.34	SEM		3.42	SEM	



Root mean square bias

•
$$RMS_{bias} = \sqrt{\frac{\sum (bias_i)^2}{n}}$$

Relative root mean square bias

• *RMS*_{bias} divided by the mean



Add relative variances

=

Add relative standard deviations squared

Magnusson, B., et al. (2012). "Routine internal- and external-quality control data in clinical laboratories for estimating measurement and diagnostic uncertainty using GUM principles." <u>Scand J Clin Lab</u> <u>Invest</u> **72**(3): 212-220.

Step	Action	Lower interval < 120 µmol/L	Higher interval > 120 μmol/L
1	Specify Measurand		nine in a serum sample
2	Quantify R _w component A control sample	s_{Rw} = 3.4 μ mol/L	CV _{Rw} =3.7 %
3	Quantify bias components	$RMS_{bias} = 5.1 \ \mu mol/L$ $u(C_{Ref}) = 0.7 \ \mu mol/L$	$RMS_{bias} = 3.0 \%$ $u(C_{Ref}) = 0.5 \%$
4	Convert components to standard uncertainty u(x)	$u(R_{w}) = s_{Rw} = 3.4 \ \mu mol/L$ $u(bias) = \sqrt{RMS_{bias}^{2} + u(C_{ref})^{2}}$ $= \sqrt{5.1^{2} + 0.7^{2}} \ \mu mol/L$ $= 5.1 \ \mu mol/L$	$u(R_w) = CV_{Rw} = 3.7 \%$ $u(bias) = \sqrt{RMS_{bias}^2 + u(C_{ref})^2}$ $= \sqrt{3.0^2 + 0.5^2} \% = 3.0 \%$
5	Calculate combined standard uncertainty, $u_{1}^{u_{1}^{2}+u_{2}^{2}}$	Standard uncertainties can be surroot of the sum of the squares $u_{\rm c} = \sqrt{u({\rm R_w})^2 + (u({\rm bias}))^2}$ $= \sqrt{3.4^2 + 5.1^2} \mu{\rm mol/L}$ $= 6.1 \mu{\rm mol/L}$	$u_{\rm c} = \sqrt{u({\rm R}_{\rm w})^2 + (u({\rm bias}))^2}$
6	Calculate expanded uncertainty, $U = 2 \cdot u_c$	The measurement result the e interval where the "true value" confidence (app. 95 %). $U = 2.6.1 \mu \text{mol/L}$ = 12.2 $\mu \text{mol/L} \approx 12 \mu \text{mol/L}$	



Thank you

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