Bias in Clinical Chemistry

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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		
Measurement	Commutable?	Commutable?	Commutable?	Commutable?	Commutable!		Patient result
procedure	reference measurement	reference measurement	Manufacturers measurement		Routine measurement in a clinical laboratory		
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							

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
U	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

в, мс	HC							
Mtd	Inst	ColD	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	20
M1	3311	PPI	332,5	3,546	2,992	1,946	2,042	24

Variance component analysis

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	Alat - 1215 P.Alat	B-998054 - CD 29 Hog	311	407 P	91 33	4,6 3,906	2,450	3,286	3,852	8				
	Ab - 1209 P-Albumin	998062 - CD29 Lig	A11	408 P	ri 34	3,6 3,781	1,253	3,665	3,608	20				
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	e CI+ Mikland	Lolakem2 - Lakemedel	311	5202 P	00	86 5.596	5 513	0,7372	0,7335	53				
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	CLEV - Bulloud	PPI - Mentorkontrol	341	6211 P	90 90	76 7,185	7,113	1,040	1,050	24				
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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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96 · HemoTrol, hög	EVF [1107 B-Erytrocyter, volymfraktion 6213 PPI	EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfraktion 6215 PPI	EVF [1107 B-Erytrocyter, volymfraktion 6216 PPI	EVF [1107 B-Erytrocyter, volymfraktion 6217 PPI	EVF [1107 B-Erytrocyter, volymfraktion 5218 PPI	EVF [1107 B-Erytrocyter, volymfraktion	n EVF [1107 B-Erytrocyter, volymfraktion 7108 PPI	EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfraktion 8211 PPI	EVF [1107 B-Erytrocyter, volymf
14 - Extern kontroll, Seronc 2 - Extern kontroll Seronc											
999 - Patientkontroll, LMC											
mun - Immunoassay, progi kem 1 - Läkemedel	EVF [1107 B-Erytrocyter, volymfraktion	EVF [1107 B-Erytrocyter, volymfraktion 8611 PPI	EVF [1107 B-Erytrocyter, volymfraktion 8711 PPI	EVF [1107 B-Erytrocyter, volymfraktion	xFc[1240 P-Järn]	xFe [1240 P-Järn] 7205 PPI	Fib [P-Fibrinogen]	Fib [P-Fibrinogen]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransfer
kem2 - Läkemedel											
kem3 - Läkemedel								ایری است این است این است است	888 		
em4 - Lakemedei onf - Koagulation	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransfer
.oa - Koagulation											
nix - Koagulation creen - Koagulation	· · · · · · · · · · · · · · · · · · ·		····· 1001 1001 ····· 1001 1001 ·····								
ston - Blodgaser	GGT [1224 P-Y-Glutamyltransferas]	GGT [1224 P-Y-Glutamyltransferas]	fGluk [1233 fP-Glukos(fastande)]	PGluk [1233 P-Glukos (fastande)]	PGluk [1233 P-Glukos (fastande)]	PGluk [1233 P-Glukos (fastande)]	Gluk-vB [vB-Glukos]	Gluk-vB [vB-Glukos]	xxHb [aB-Hemoglobin]	xxHb [sB-Hemoglobin]	Hb [1108 B-Hb(Hemoglobin)]
endo1 - Endokrinologi			2300 PM	234 FFI						4000 PP1	
alk - Alkoholer		Naa, Kalinkakaa <mark>18.989a 1</mark> 8	nan <mark>a n n n n - N - N - N - N - N - N - N - N - N -</mark>	~~ ~~ ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	a-a ^g g-agaaa ^s	∽≈≈⋑ <mark>⋑</mark> ⊸≈⋑⋑⋑⋑⋍ <mark>⋑</mark>	agailesteriki kileseeneli join	a		뽜 튑쥥뉵뭑롎쥥뭑뭑륋쥥뭑뭑붱뉵렮	
odt - CD-Transferrin	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]
csv - Proteinanalyser i spi fores1 - Elfores		3111 PPI			3511 PPI	3611 PPI		3811 PPI	3911 PPI	4011 PPI	40r PPI
fores2 - Elfores	agaggg <mark>ggg</mark> g_a <mark>s</mark> aaaagaag	─────────────────────────────────────		ana ang ang ang ang ang ang ang ang ang	ਸ਼ਗ਼ਗ਼ਗ਼ਗ਼ਗ਼ <mark>ੑਗ਼</mark> ਗ਼ਗ਼ਗ਼ਗ਼ਗ਼	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		aan <mark>i la intanan 488.annan</mark>	laanaa <mark>haladaalla_n Haasaal</mark>	∽⋬⋬⋬⋬⋓ <mark>⋰</mark> ⋓⋍⋻⋴∼⋳⋍⋳⋍∊	
fores3 - Elfores hem4000 - Hematologi	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]
ngc · Hemocue	408 PPI	4111 PPI	415 PPI	4311 PPI	4411 PPI	4612 PPI	5202 PPI	6210 PPI	6211 PPI	6212 PPI	6213 PPI
oh Iohexol	aaagg <mark>abe</mark> gabegabegabe	antikaniti kan katalatan inisi	afia <mark>-</mark> andudududadad	Restalland Sevenation Restant	-andiina <mark>) -</mark> ann-annanai <mark>l</mark>	and the state of the second	28		Para a provinsi da anti-		<u>⋳∼⋳⋰</u> ⋳⋳⋳ <mark>⋰</mark> ∼⋳∼⋴⋳
koaA - Koagulation	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin]]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]
toaB - Koagulation	6214 PPI	6215 PPI	6216 PPI	6217 PPI	6218 PPI	6219 PPI	7108 PPI	7570 PPI	8011 PPI	8211 PPI	8311 PPI
ip1 - Lipoprotein ip2 - Lipoprotein			agg <mark>g a</mark> ssagggga								
nia - Albumin i urin, låg ni	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	Hb [1108 B-Hb(Hemoglobin)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono :
prot - P-protein et - Betikulocuter	8511 PPI	8611 PPI	8711 PPI	8911 PPI	2404 PPI	3570 PPI	3670 PPI	3770 PPI	3870 PPI	3975 PPI	4170 PPI
upr - U-Protein											
etho - MMA + Homocyste	xÖHbA1c [Hb(B]-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B]-HbA1c (Mono S)]	xÖHbA1c [Hb(B]-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S11	xÖHbA1c [Hb(B]-HbA1c (Mono S)]	xÖHbA1c [Hb(B]-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S1)	xÖHbA1c [Hb(B)-HbA1c (Mono 3
AKOA1 - Koagulation, spe AKOA2 - Koagulation, spe	4370 PPI	4470 PPI	6382 PPI	6383 PPI	6385 PPI	6386 PPI	6388 PPI	8070 PPI	8170 PPI	8270 PPI	8370 PPI
em1 Läkemedel						-			— ——		
em2 · Lakemedel	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)1	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B)-HbA1c (Mono S)]	xÖHbA1c [Hb(B]-HbA1c (Mono S)]	pHbA1clF [B-HbA1c (IFCC) pv1	pHbAtclF (B-HbAtc (IFCC) pv1	pHbA1clF [B-HbA1c (IFCC) pv1	xHDLKol [1228 P-HDL-Kolesterol]	xHDLKol [1228 P-HDL-Kolesterol]	xHDLKol [1228 P-HDL-Kolestero
Mentorkontroll	8570 PPI * ********************************	8670 PPI	8770 PPI	8870 PPI	8970 PPI	2652 PPI	6380 PPI	8470 PPI	2500 PPI	254 PPI	3803 PPI
DWN1 - Downs screening								فيسمد ويهي التسعيد ويهي فمسعد الكك أنكلت			
AVAID DOWNS SCIEDURING		xHDLKol [1228 P-HDI -Kolesterol]	xHDLKol [1228 P-HDI -Kolestero ¹¹	xHDLKol [1228 P-HDL-Kolesterol]	xHDLKol [1228 P-HDL-Kolesterol]	xHDLKol [1228 P-HDI -Kolesterol]	xHDLKol [1228 P-HDI -Kolesterol]	xHDLKol [1228 P-HDL-Kolesterol]	xHDLKol [1228 P-HDI -Kolesterol]	xHDLKol [1228 P-HDL-Kolesterol]	xHDLKol [1228 P-HDL-Kolectore
JWIN3 - Downs screening	XITULKOI I IZZO PHITUL-Kolesterou	and a second Will	the second	coor ppi	SEOS DOL	6607 001	6602 DDI	6609 PDI	7205 PDI	7006 001	8603 PDI
asub - Protein	4403 PPI	6600 PPI	6601 PPI								

Results panel

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\varTheta variance	analys									
File Edit						, A	;			
2000-01-01	- 2001-08-11	ĺκι	L\Klinisk ke	mi∖KS Klin k	emi (KSKK) 🖬	LUSTIX2	0. UGlul	cos íren	nsaì	
🗆 Hse NPH	components	N.	Lid	Method	Mean	cv	CV C	N	FirstDay	LastDay
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	d series only	KI	L\Klinisk ke	mi∖KS Klin k	emi (KSKK) : G	GT20, SG	σT			
Separate :	subgroups [View]	<u> N</u>	Lid	Method	Mean	CV	CV C	N	FirstDay	LastDay
Ev Kl		1	9999110	2002	1,162	2,96	2,96	572	2001-01-10	2001-06-08
	(Immunologi		9999130	2002	5,442	8,75	8,75	155	2001-01-10	2001-06-08
- Kiiriist	k minunologi k fassalkalaai		9999160	2001	1,165	5,17	5,17	392	2001-01-10	2001-06-08
	k rarmakologi		9999170	2001	5,622	6,88	6,88	137	2001-01-10	2001-06-07
	K KEMI		9999180	2003	1,180	3,01	3,01	267	2001-01-10	2001-06-07
	S Klin kemi (DSKK)		9999180	2007	1,200			1	2001-05-01	2001-05-01
	xtern Verksamhet		9999184	2007	1,167	2,77	2,77	181	2001-01-10	2001-06-08
	S Klin kemi (KSKK)		9999190	2003	5,489	6,55	6,55	111	2001-01-10	2001-06-08
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÷∙N	S Klin kemi (NSKK)		9999194	2007	5,636	7,64	7,64	101	2001-01-10	2001-06-08
i All results		I								
		KI	L\Klinisk ke	mi∖KS Klin k	emi (KSKK) : H	IAPTO20,	PHapto	globin ((mass)	
		<u> N</u>	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	2001-06-07
-			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
			NRP-2-1-1-	- BKC KR. L				(
			Lid	Method	emi (nonn) : r Mean	CV	niauigun n vn	(mass) N	FirstDav	LastDav
		l a -	9999100	2014	59.59	5.07	5.07	367	2001-01-10	2001-06-08
			9999100	2014	58,85	2.06	2.06	240	2001-01-10	2001-06-07
			9999100	2016	58.52	2.13	2.13	389	2001-01-10	2001-06-08
			9999400	2014	119.6	1.88	1.88	389	2001-01-10	2001-06-08
		1	9999400	2015	120.4	1.78	1.78	245	2001-01-10	2001-06-07
		1	9999400	2016	118.0	1.98	1.98	410	2001-01-10	2001-06-08
		1	9999500	2014	59,70	1,53	1,53	27	2001-02-23	2001-04-23
		1	9999500	2015	59,00	1,23	1,23	20	2001-02-23	2001-04-23
			9999500	2016	58,82	1,54	1,54	28	2001-02-23	2001-04-24
			9999600	2014	120,3	0,930	0,930	30	2001-02-23	2001-04-23
			9999600	2015	120,9	0,802	0,802	19	2001-02-23	2001-04-23
			9999600	2016	119,3	1,42	1,42	31	2001-02-23	2001-04-24
		KI	L\Klinisk ke	mi∖KS Klin k	emi (KSKK) : H	ICG24, FL	X00366			
		N	Lid	Method	Mean	CV	CV C	N	FirstDay	LastDay
		1	9999370	2006	2,840			1	2001-04-30	2001-04-30
		1	9999380	2004	4,580	37,2	37,2	218	2001-01-09	2001-06-07
			9999380	2006	5,145	30,2	30,2	191	2001-01-10	2001-06-08
			9999390	2004	24,42	8,16	8,16	228	2001-01-09	2001-06-07
•	▶									

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

In Turkish

<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 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.





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

correction need resources. However it should be

considered if the small bias should be taken into

If bias is significant then the best approach, it

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

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

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

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

would have been without correction.

included in uncertainty

account in the MU

method.

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	Higher interval
		< 120 µmol/L	> 120 µmol/L
1	Specify Measurand	Concentration of creat delivered to	inine in a serum sample the laboratory.
2	Quantify R _w component A control sample	$s_{Rw} = 3.4 \ \mu mol/L$	CV _{Rw} =3.7 %
3	Quantify bias components	$ m RMS_{bias}$ = 5.1 $\mu mol/L$ $u(C_{ m Ref})$ = 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 s root of the sum of the squares $u_{c} = \sqrt{u(R_{w})^{2} + (u(bias))^{2}}$ $= \sqrt{3.4^{2} + 5.1^{2}} \mu mol/L$ $= 6.1 \mu mol/L$	summed by taking the square $u_{\rm c} = \sqrt{u(R_{\rm w})^2 + (u(\text{bias}))^2}$ $= \sqrt{3.0^2 + 3.7^2} \% = 4.8\%$
	Calculate emanded	The measurement result the	expanded uncertainty gives an



Thank you

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