The linkage between method validation, traceability and measurement uncertainty

Wolfhard Wegscheider

General and Analytical Chemistry
Montanuniversität Leoben, Austria

wegschei@unileoben.ac.at

„The program“:

- Method validation
- Traceability
- Uncertainty
- Is there a connection prescribed by logic?
- Is there a hierarchy or time sequence?
- What are the tools of the trade?

The sequence:

- Customers have to make decisions
- Decisions are correct or incorrect
- „Good" correctness requires small uncertainty (⇒ small target uncertainty)
- Method development is aimed at target uncertainty
- Validation has many facets/...
- Uncertainty of measurement from separate components
- Uncertainty is limited by traceability

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What is required for decisions?

- Measurement results

(measured quantity value AND measurement uncertainty)

- Decision on state
  - Acceptable
  - Not acceptable
  - (no decision)
- (regulatory) limits
- Decision rule

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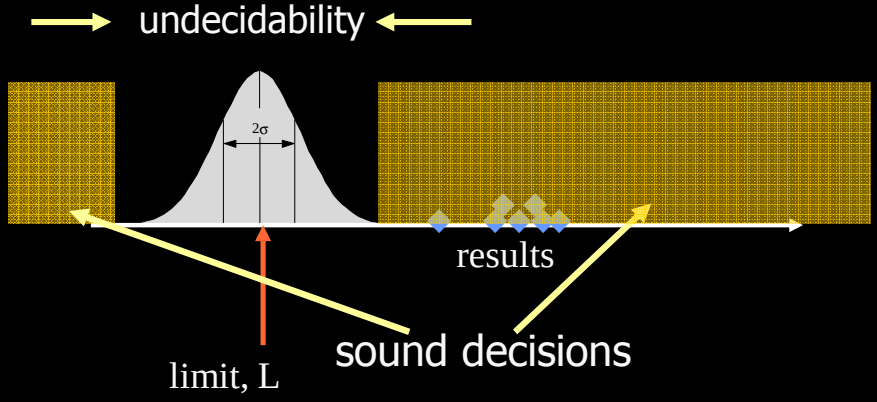
Uncertainty causes a region of undecidability



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Sometimes this is mirrored by modern legislation:

COMMISSION DIRECTIVE 2009/90/EC of 31 July 2009 … technical specifications for chemical analysis and monitoring of water status

„Member States shall ensure that the minimum performance criteria for all methods of analysis applied are based on an uncertainty of measurement of 50 % or below (k = 2) estimated at the level of relevant environmental quality standards and a limit of quantification equal or below a value of 30 % of the relevant environmental quality standards."

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Different roles of method validation

- Establish performance characteristics
  - Linearity
  - Limits of detection/determination
  - Precision: repeatability, intermediate reproducibility
  - Effect of concomitants
  - Trueness
- Identify influence coefficients: robustness
- Present data for approval of method
- Produce control limits for everyday operation

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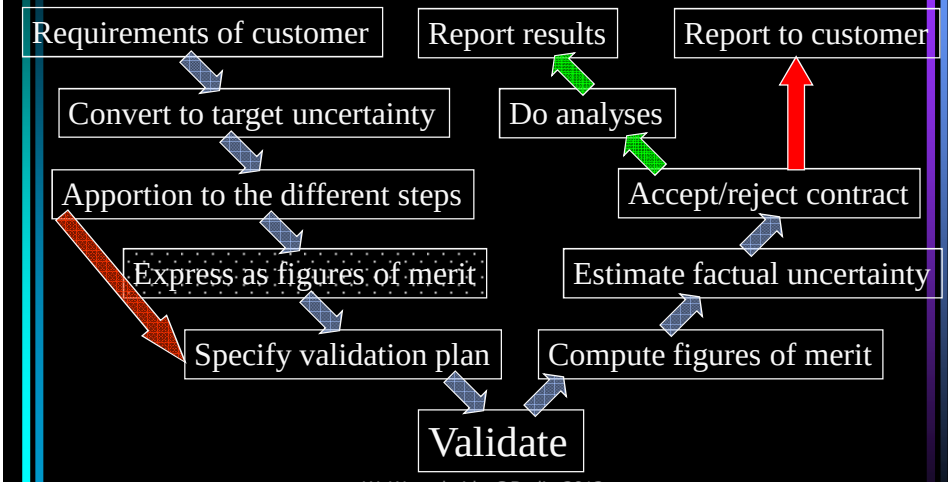
Validation starts out from the customer´s needs



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Metrological traceability:

property of a **measurement result** whereby the result can be related to a reference through a documented unbroken chain of **calibrations,** each contributing to the **measurement uncertainty**

(VIM ISO/IEC JCGM 200:2012)

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Two key components to traceability of a measurement result:

- standards $\pm u_{st}$

- uncertainty $\pm u_{pr}$

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combined uncertainty:

$$u_x = \sqrt{u_{st}^2 + u_{pr}^2}$$

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Two „types" of references:

1. with *little* influence on final result
2. with *large* influence on final result

Ad 1)

- large uncertainty on reference contributes little to uncertainty
- poor control to this reference produces but a small deviation

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Two „types" of references:

1. with *little* influence on final result
2. with *large* influence on final result

Ad 2)

- large uncertainty on reference contributes a lot to uncertainty
- poor control to this reference produces a large deviation

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What is required ?

- A (complete) model of measurement

$$x_{i,p,T,V,m} = f(x_0)\big|_{p,T,V,m} + \varepsilon_i$$

x....result

f...model

x_o...value of standard

ε_i...random error of measurement i

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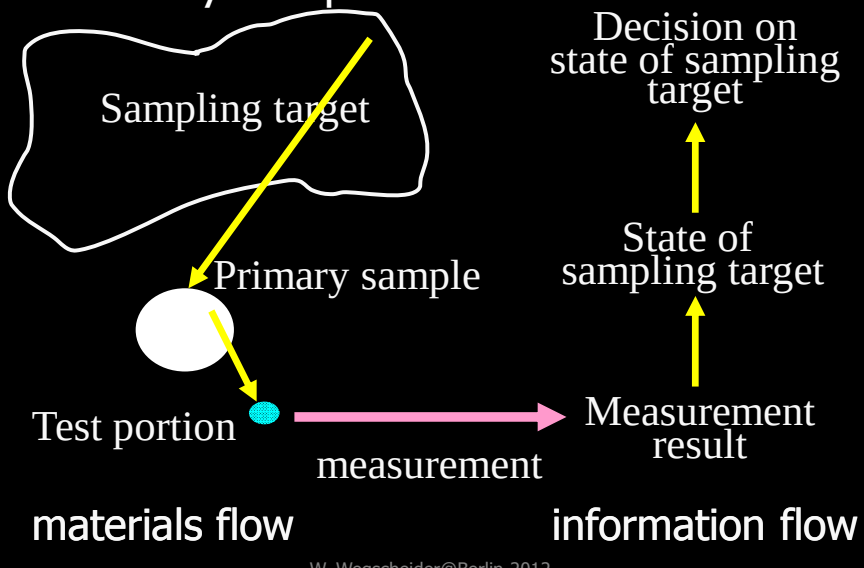
The analytical process:



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Advanced Methods for the Determination of Uncertainty: M.C.

- Scientific Motivation
  - Large uncertainties
  - „natural" limits: upper and lower end
  - Deeper understanding
- GUM Supplement 1

  "Propagation of distributions using a Monte Carlo method, JCGM 101:2008, http://www.bipm.org/en/publications/guides/gum.html

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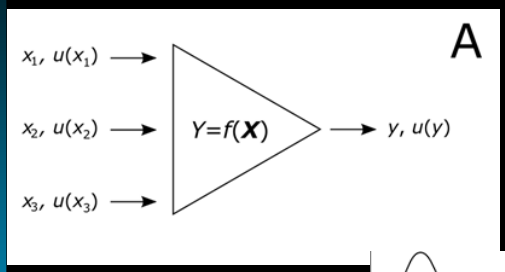
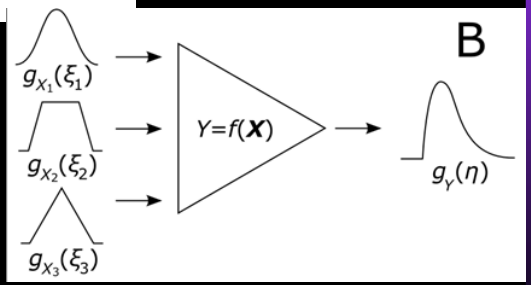
Uncertainty of measurement:



what´s new?

A old
B new



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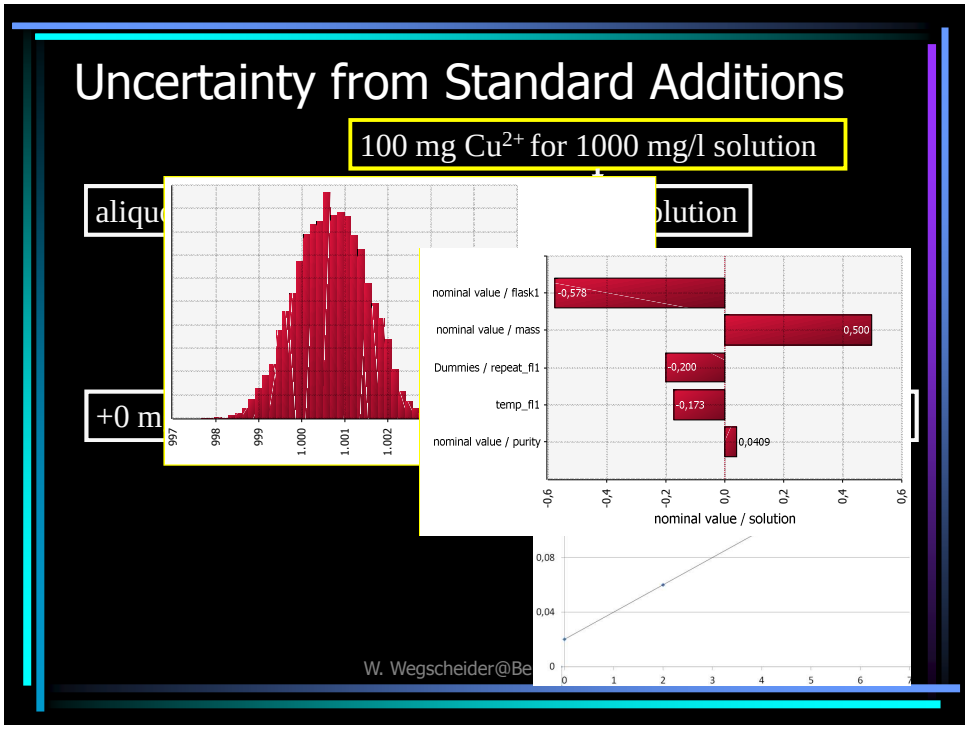
Uncertainty from Standard Additions
100 mg Cu2+ for 1000 mg/l solution
nominal value / flask1
nominal value / mass
Dummies / repeat_fl1
temp_fl1
nominal value / purity
-0,578
0,500
-0,200
-0,173
0,0409
nominal value / solution
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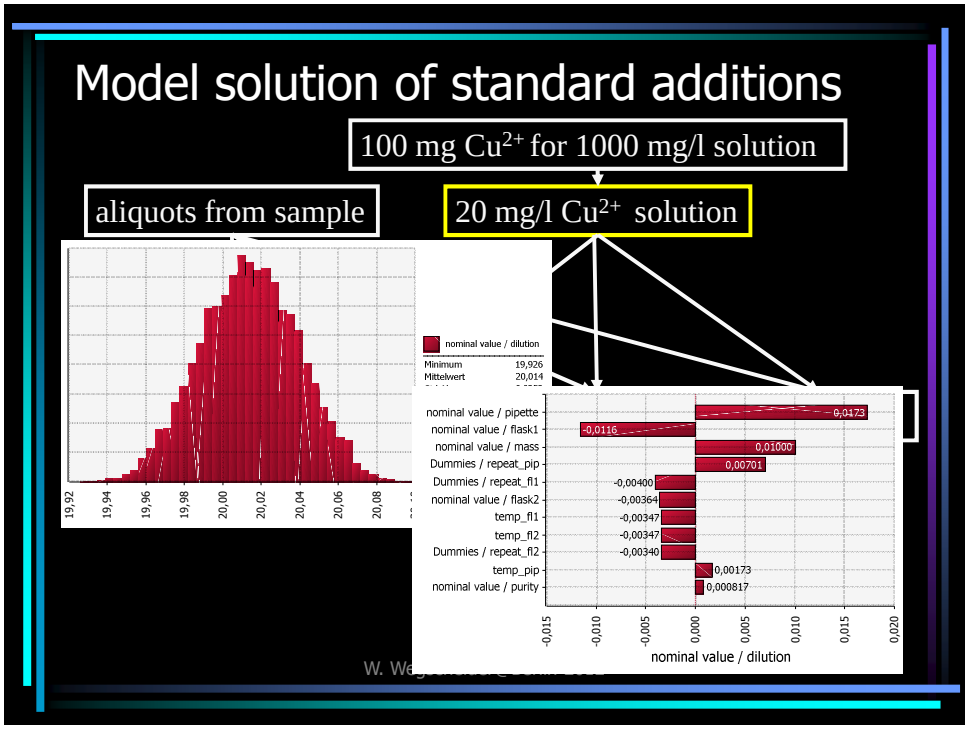
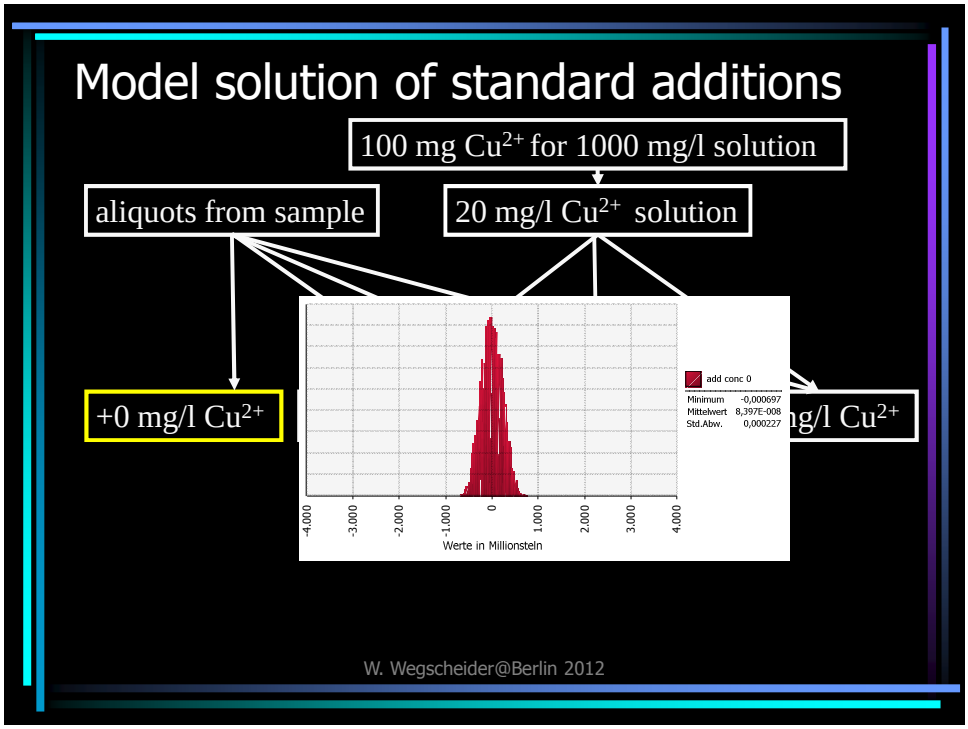

Model solution of standard additions
100 mg Cu2+ for 1000 mg/l solution
aliquots from sample
20 mg/l Cu2+ solution
nominal value / dilution
Minimum 19,926
Mittelwert 20,014
nominal value / pipette
nominal value / flask1
nominal value / mass
Dummies / repeat_pip
Dummies / repeat_fl1
nominal value / flask2
temp_fl1
temp_fl2
Dummies / repeat_fl2
temp_pip
nominal value / purity
0,0173
-0,0116
0,01000
0,00701
-0,00400
-0,00364
-0,00347
-0,00347
-0,00340
0,00173
0,000817
nominal value / dilution


Model solution of standard additions
100 mg Cu2+ for 1000 mg/l solution
aliquots from sample
20 mg/l Cu2+ solution
+0 mg/l Cu2+
add conc 0
Minimum -0,000697
Mittelwert 8,397E-008
Std.Abw. 0,000227
-4.000
-3.000
-2.000
-1.000
0
1.000
2.000
3.000
4.000
Werte in Millionsteln
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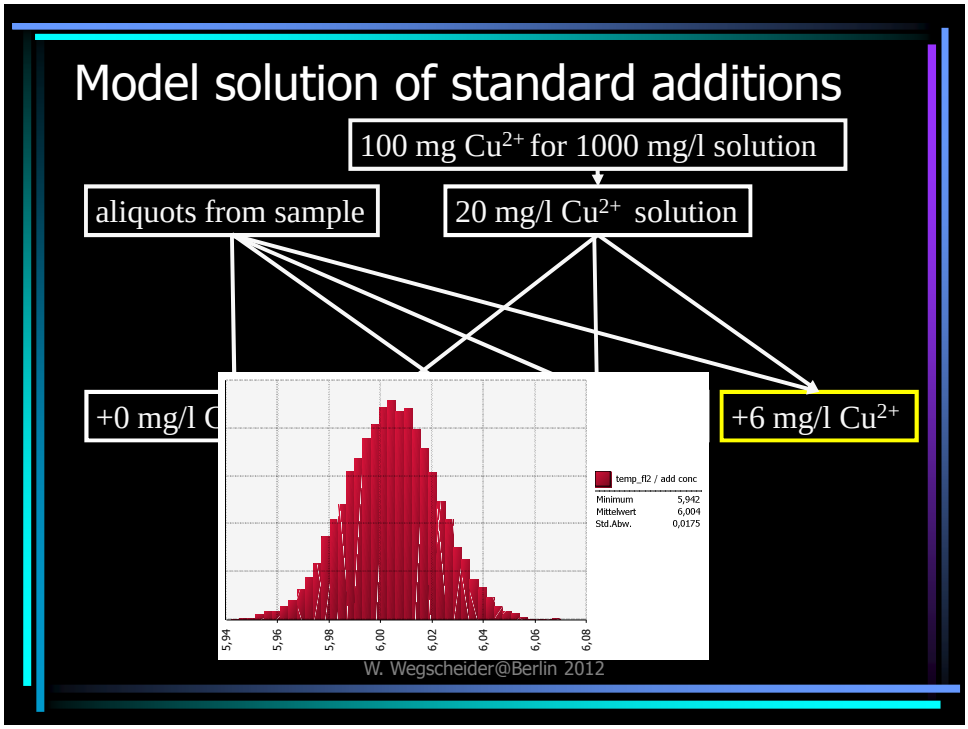
Model solution of standard additions
100 mg Cu2+ for 1000 mg/l solution
aliquots from sample
20 mg/l Cu2+ solution
+0 mg/l C
+6 mg/l Cu2+
temp_fl2 / add conc
Minimum 5,942
Mittelwert 6,004
Std.Abw. 0,0175
5,94
5,96
5,98
6,00
6,02
6,04
6,06
6,08
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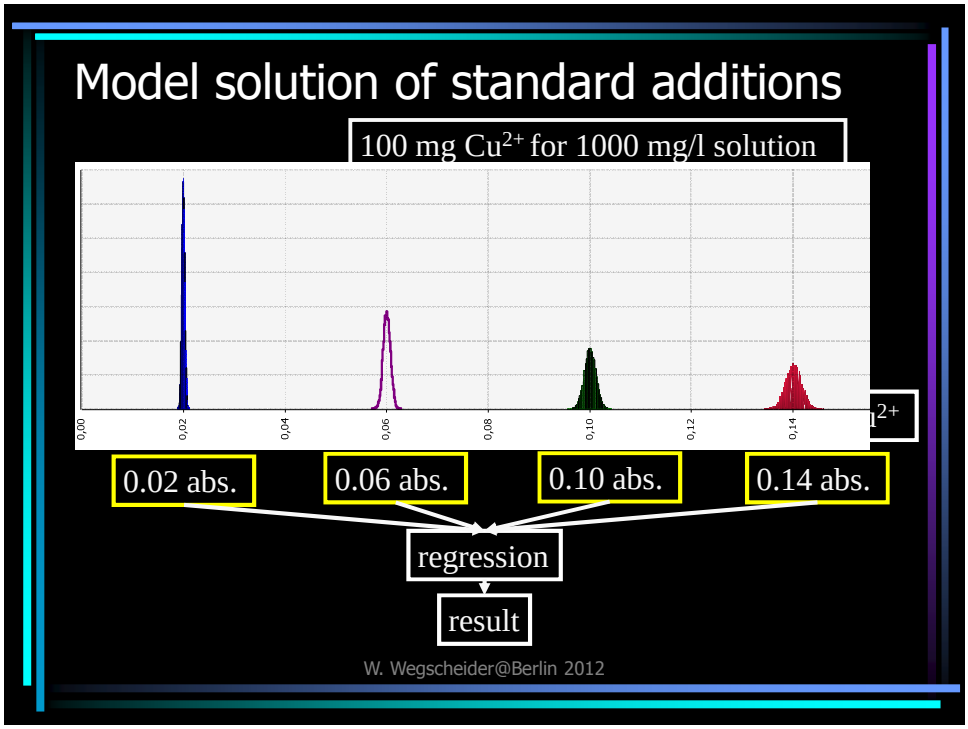
Model solution of standard additions
100 mg Cu2+ for 1000 mg/l solution
0,00
0,02
0,04
0,06
0,08
0,10
0,12
0,14
0.02 abs.
0.06 abs.
0.10 abs.
0.14 abs.
regression
result
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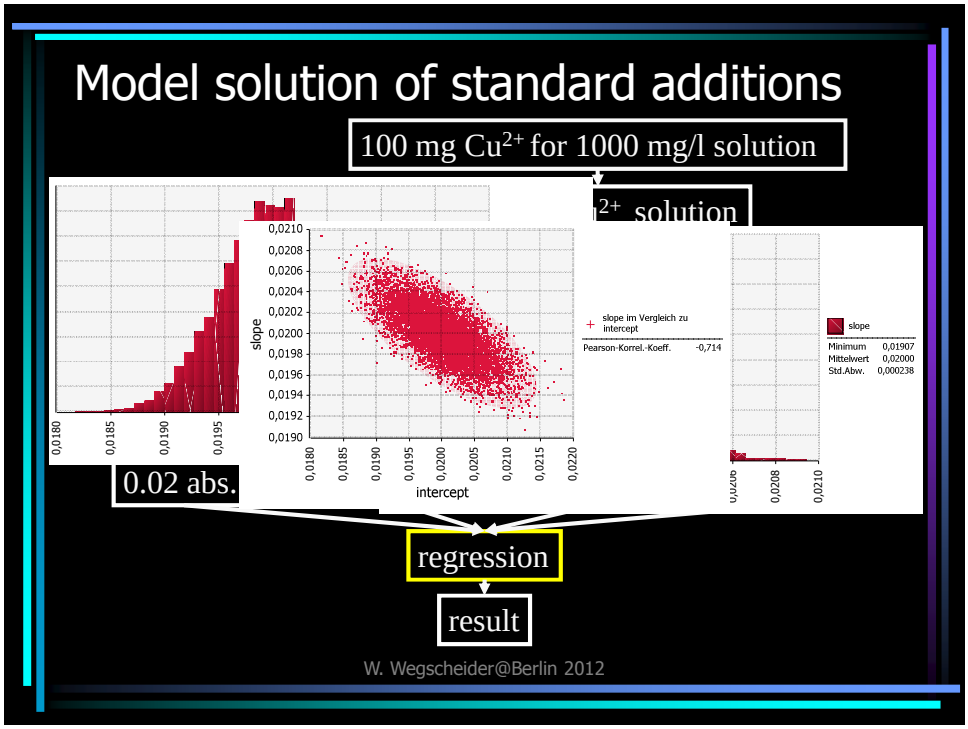
Model solution of standard additions
100 mg Cu2+ for 1000 mg/l solution
solution
0,0180
0,0185
0,0190
0,0195
0,0210
0,0208
0,0206
0,0204
0,0202
0,0200
0,0198
0,0196
0,0194
0,0192
0,0190
slope
0,0180
0,0185
0,0190
0,0195
0,0200
0,0205
0,0210
0,0215
0,0220
intercept
slope im Vergleich zu intercept
Pearson-Korrel.-Koeff. -0,714
slope
Minimum 0,01907
Mittelwert 0,02000
Std.Abw. 0,000238
0,0206
0,0208
0,0210
0.02 abs.
regression
result
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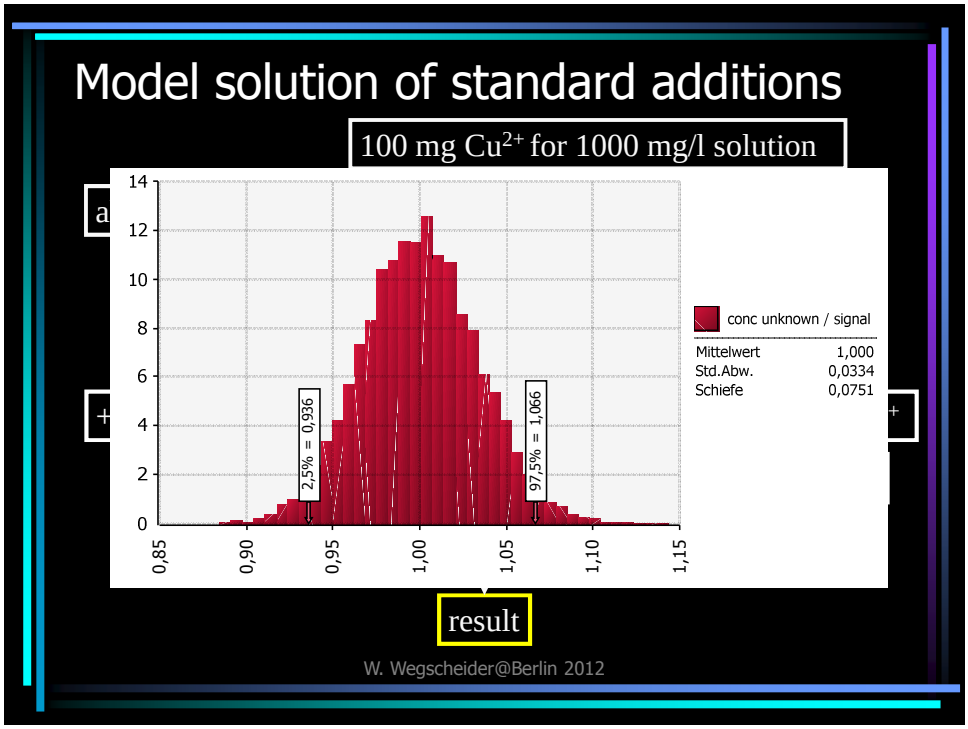
Model solution of standard additions
100 mg Cu2+ for 1000 mg/l solution
a
+
14
12
10
8
6
4
2
0
0,85
0,90
0,95
1,00
1,05
1,10
1,15
2,5% = 0,936
97,5% = 1,066
conc unknown / signal
Mittelwert 1,000
Std.Abw. 0,0334
Schiefe 0,0751
result
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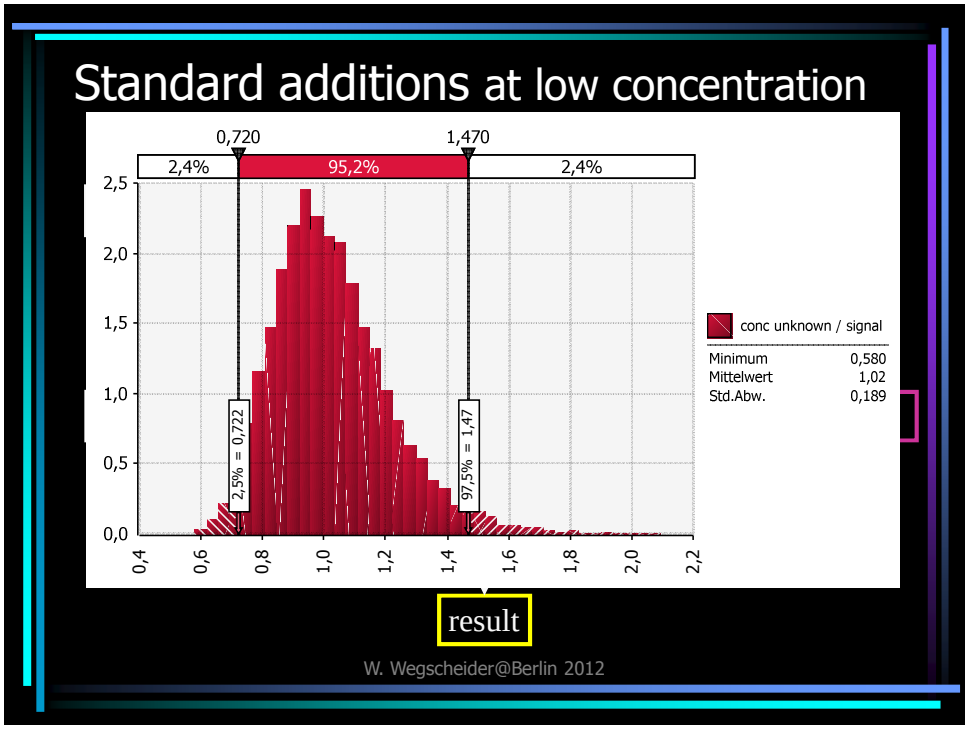
Standard additions at low concentration
0,720
1,470
2,4%
95,2%
2,4%
2,5
2,0
1,5
1,0
0,5
0,0
0,4
0,6
0,8
1,0
1,2
1,4
1,6
1,8
2,0
2,2
2,5% = 0,722
97,5% = 1,47
conc unknown / signal
Minimum 0,580
Mittelwert 1,02
Std.Abw. 0,189
result
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Definition of measurand:

- Loose ⇒ Simple procedure
- Tight ⇒ Involved procedure
- Deficiencies in definition of measurand are mapped as separate contribution in measurement uncertainty… but how?
- Sampling problem to encompass population (and not just the sample/specimen)

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Some linkage …. in summary:

- Target uncertainty defines procedure
- Procedure and traceability define uncertainty of the definition of the measurand
  - „more" procedure ⇒ „less" uncertainty
- Influence factors in validation become components of uncertainty
- Traceability limits uncertainty
- Uncertainty of references contribute to uncertainty of measurement

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- No uncertainty without traceability
  - Uncertainties of standards would be „lost"
- No uncertainty without validation
  - No influence factors identified
  - No size estimate for influence factors from references (⇒ traceability!!)

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Literature

- **International Vocabulary of Metrology – Basic and General Concepts and Associated Terms, VIM, 3rd edition, 2007** Download: http://www.bipm.org/en/publications/guides/vim.html
- **Evaluation of measurement data – Guide to the expression of uncertainty in measurement**, JCGM 100:2008 (GUM 1995 with minor corrections) Download: http://www.bipm.org/en/publications/guides/gum.html
- Eurachem Guide **The Selection and use of Reference Materials** (2002) Download: http://www.eurachem.org/guides/EEE-RM.htm
- Eurachem Guide **Quantifying Uncertainty in Analytical Measurement**, 3rd Ed. (2012) download: http://www.eurachem.org/guides/quam.htm
- Eurachem Guide **Use of Uncertainty Information in compliance assessment** (2007) download: http://www.eurachem.org/guides/compliance.htm
- Eurachem Guide **The Fitness for Purpose of Analytical Methods. A Laboratory Guide to Method Validation and Related Subjects** (1998) download: http://www.eurachem.org/guides/mval.htm

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