CORESTA Joint Study Groups Meeting
Smoke Science / Product Technology
2011 - Graz, Austria

Determination of r&R using expression of smoke constituent level per unit amount of nicotine

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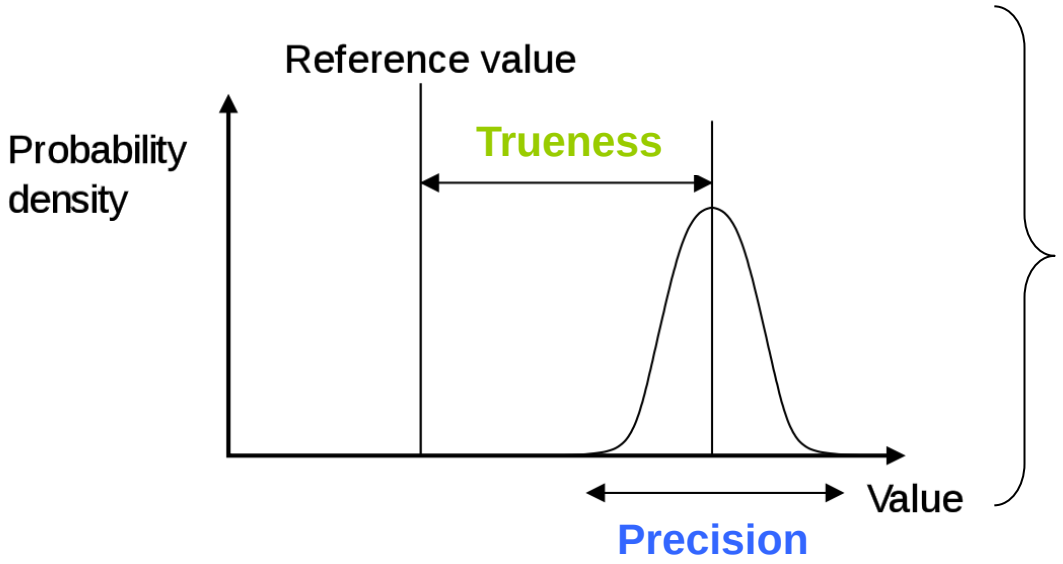
Outline

- Collaborative Study process (raw data)
- Collaborative Study process (ratio)
  - Paired measurements
  - Unpaired measurements
- Assessment of r&R for NNN/Nic
- Conclusions
- Alternative approaches

Definitions

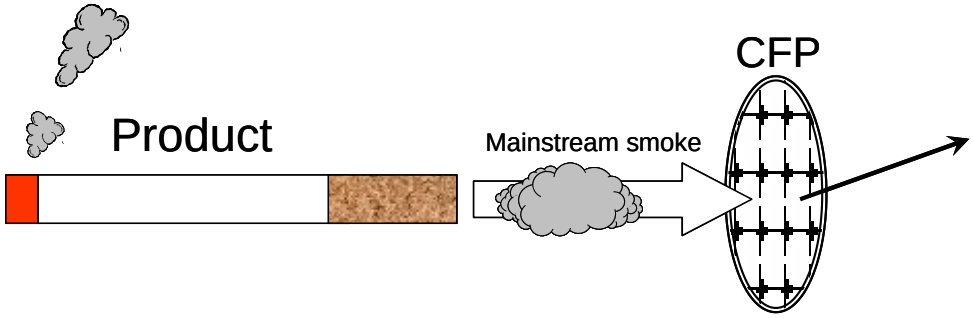
The relevance of method performance is defined by indicators



Collaborative study is a recognized method to evaluate these indicators

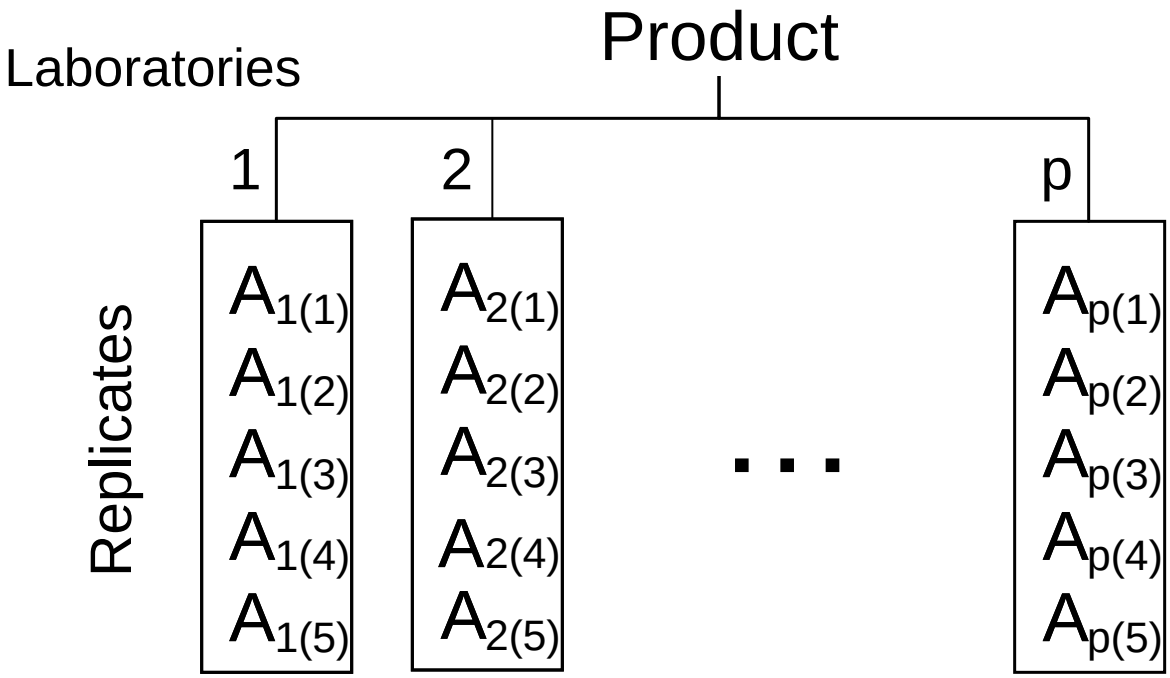
2 terms to define the **precision** of a method under 2 circumstances of replication: **repeatability** and **Reproducibility**.

Collaborative Study (raw data for A)

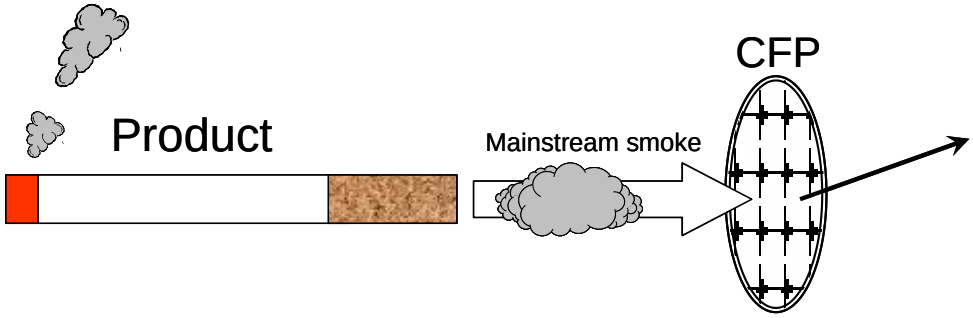


- Minimum number of laboratory: p=8 reporting valid data for each material
- Minimum number of replicates: n=2 if within-laboratory repeatibility is required

p laboratories (from 1 to p)
5 replicates per laboratory



Collaborative Study (raw data for A)



p laboratories (from 1 to p)
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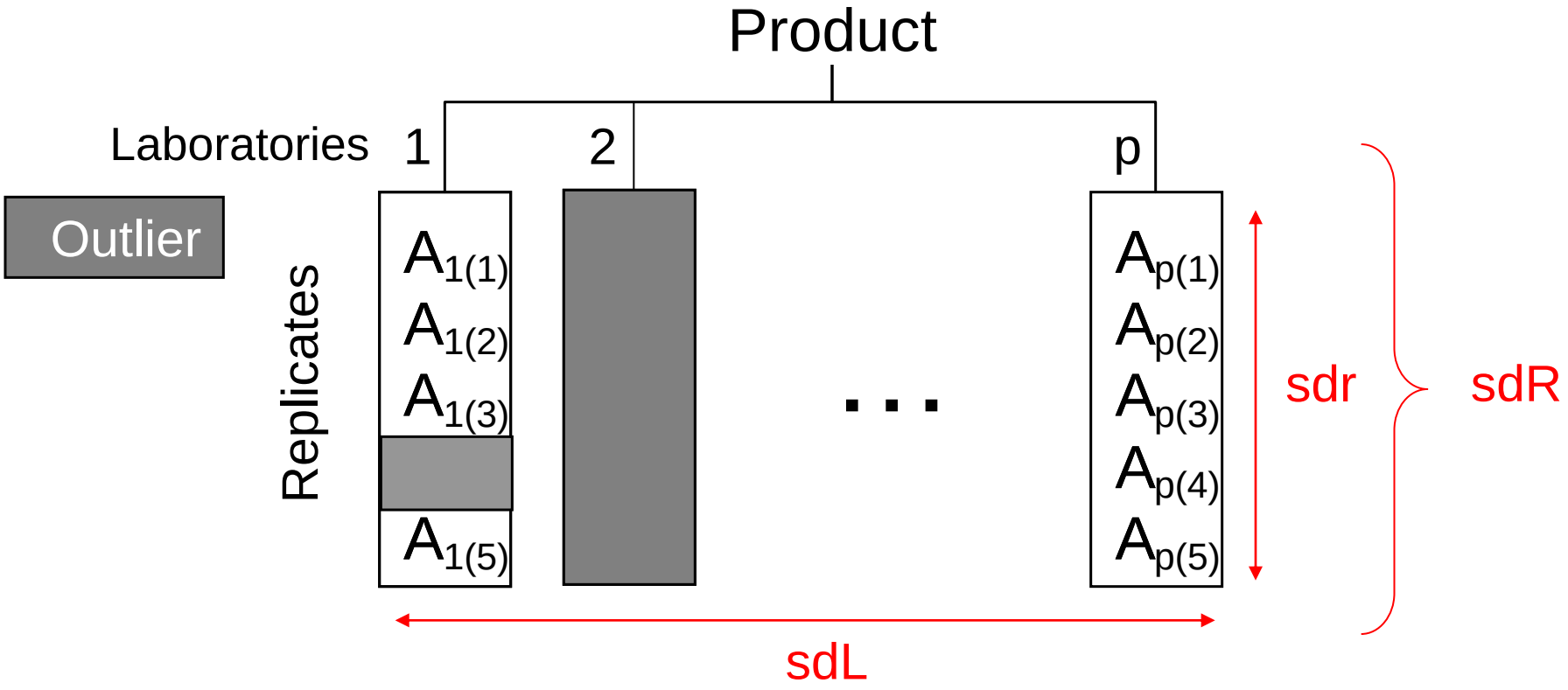
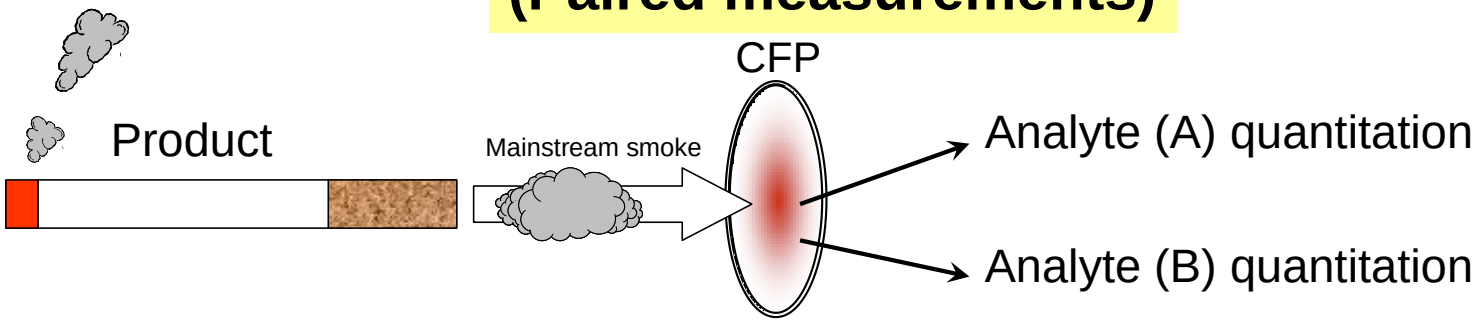
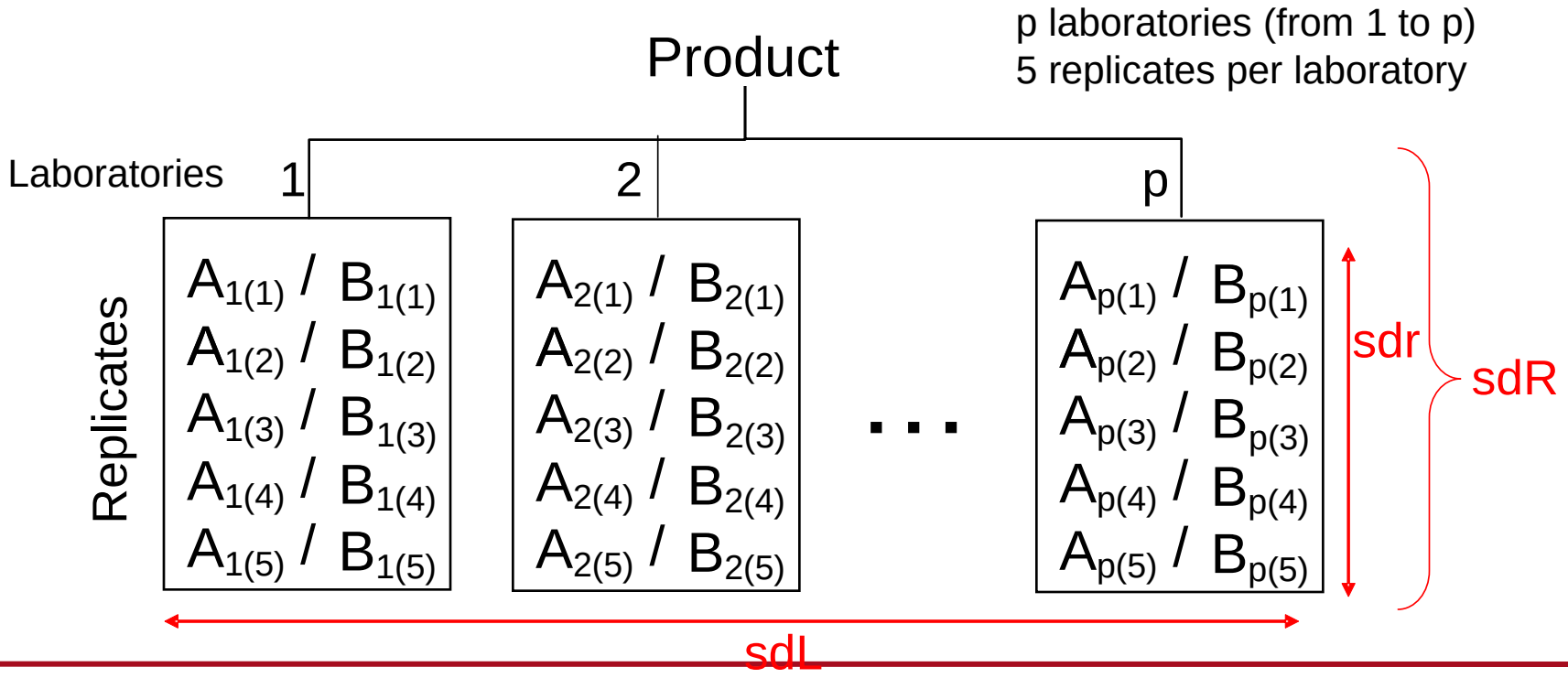


Collaborative Study (ratio A/B)

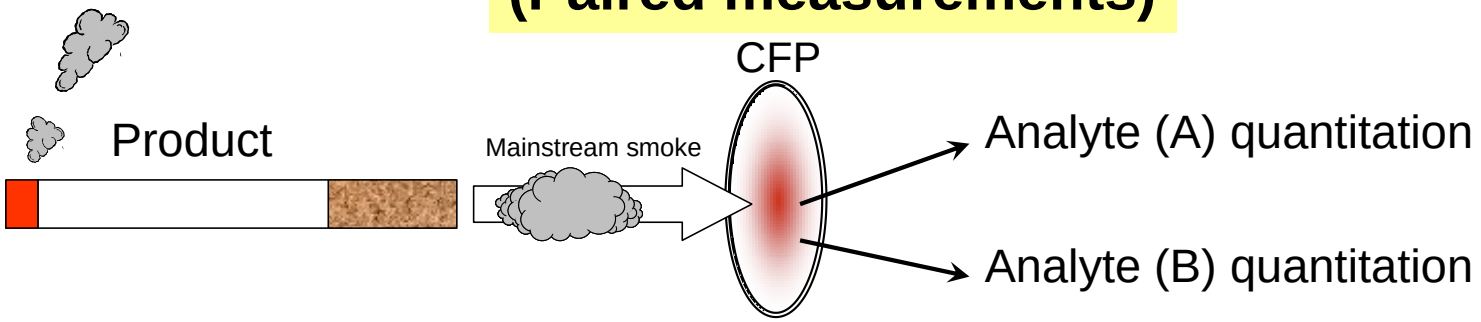
(Paired measurements)



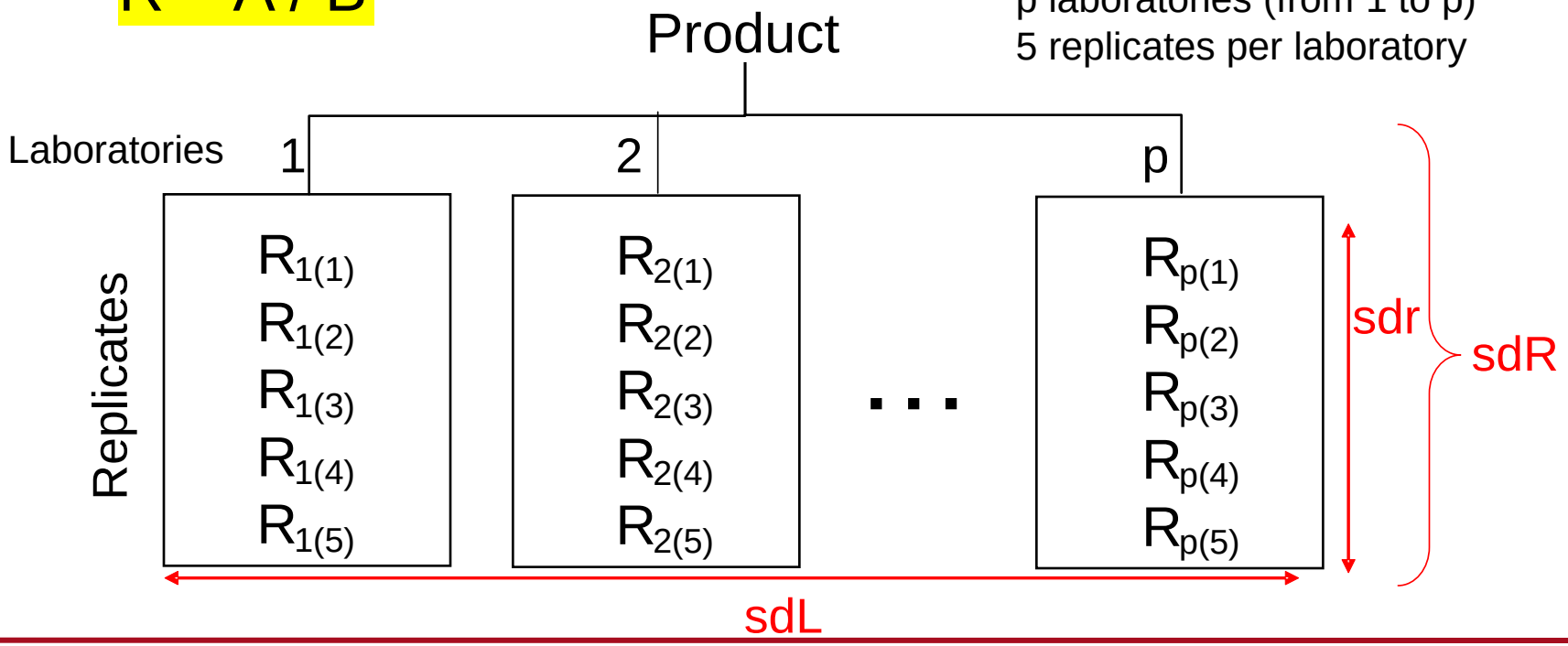


Collaborative Study (ratio A/B)

(Paired measurements)



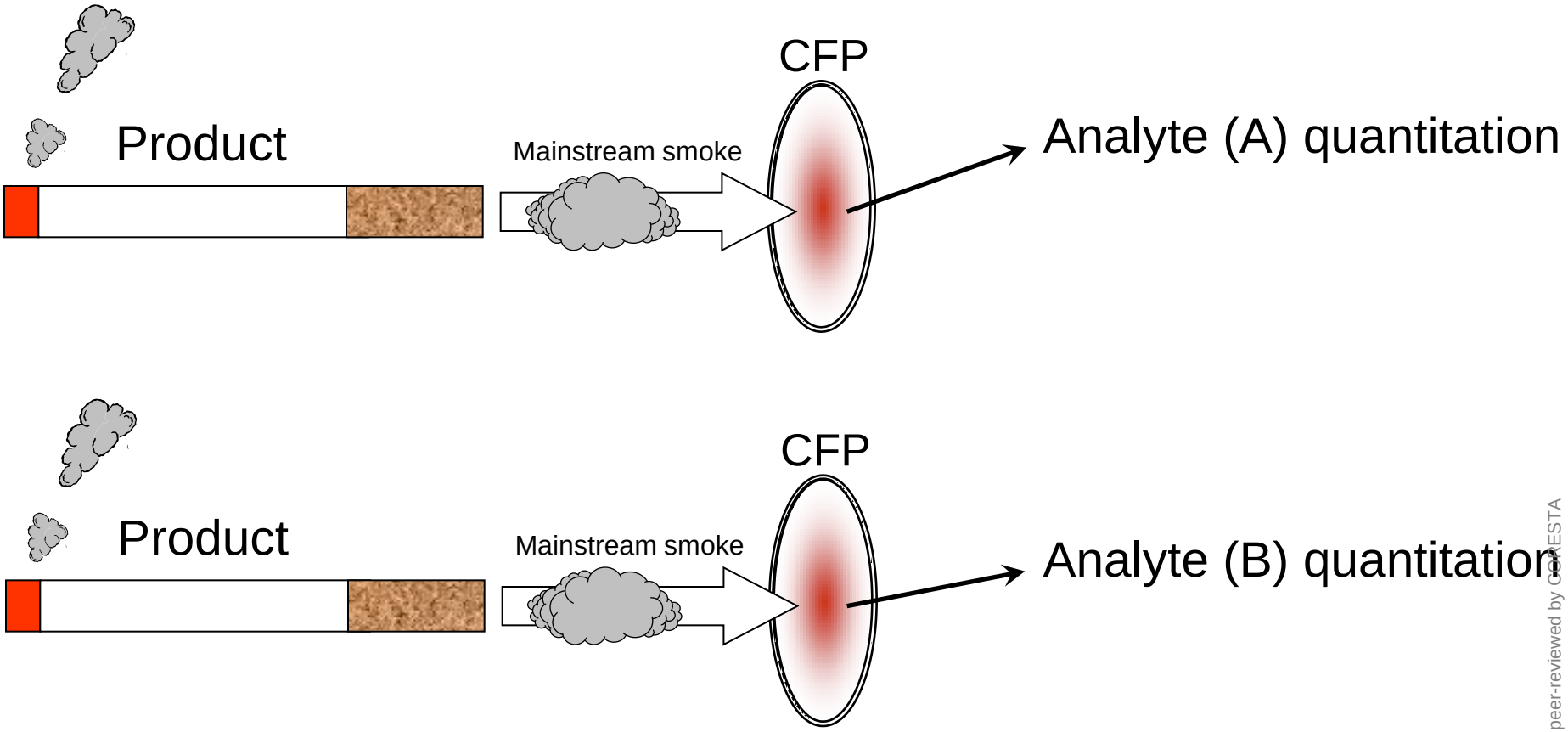
$R = A / B$



With paired measurements the ratio can be considered as raw data

Collaborative Study (ratio A/B)

(Unpaired measurements)

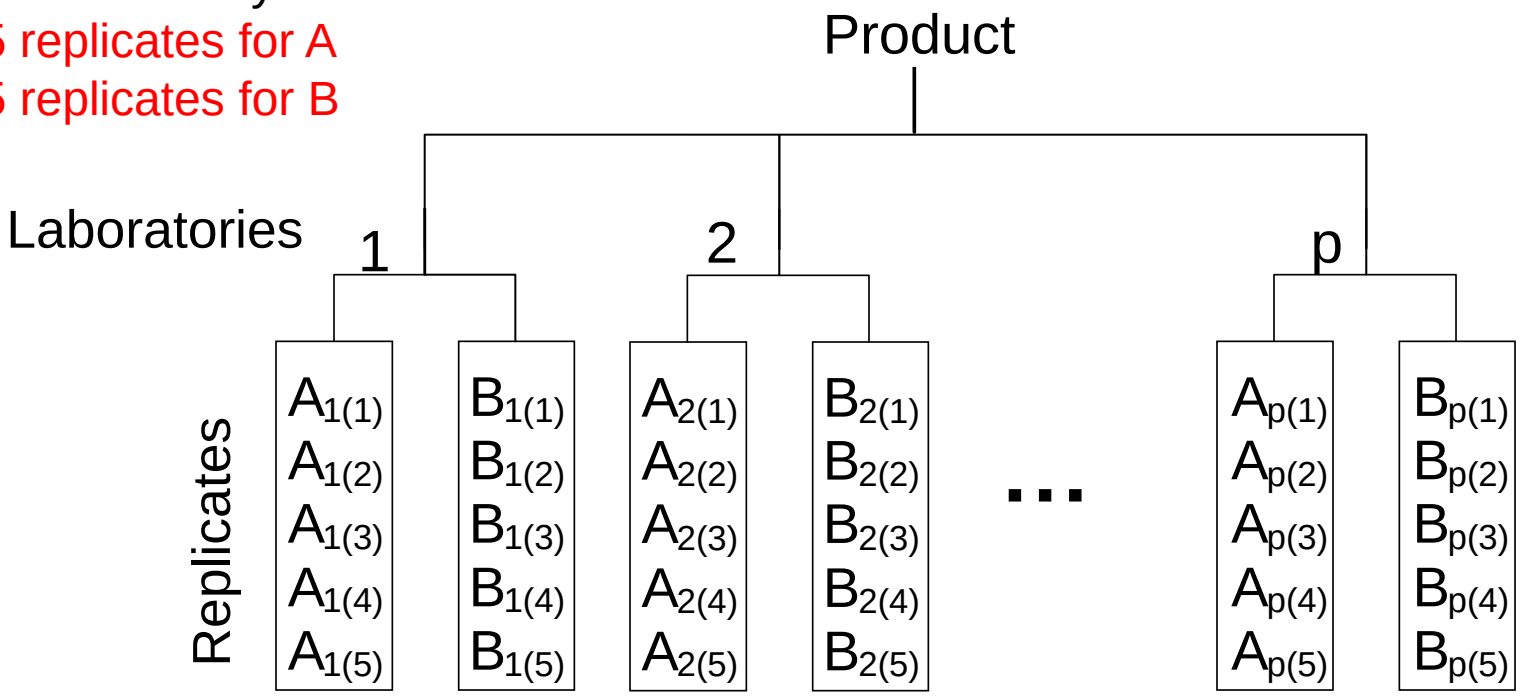


Collaborative Study (ratio A/B)

(Unpaired measurements)

p laboratories (from 1 to p)

per laboratory:
5 replicates for A
5 replicates for B



How to compute the ratio?

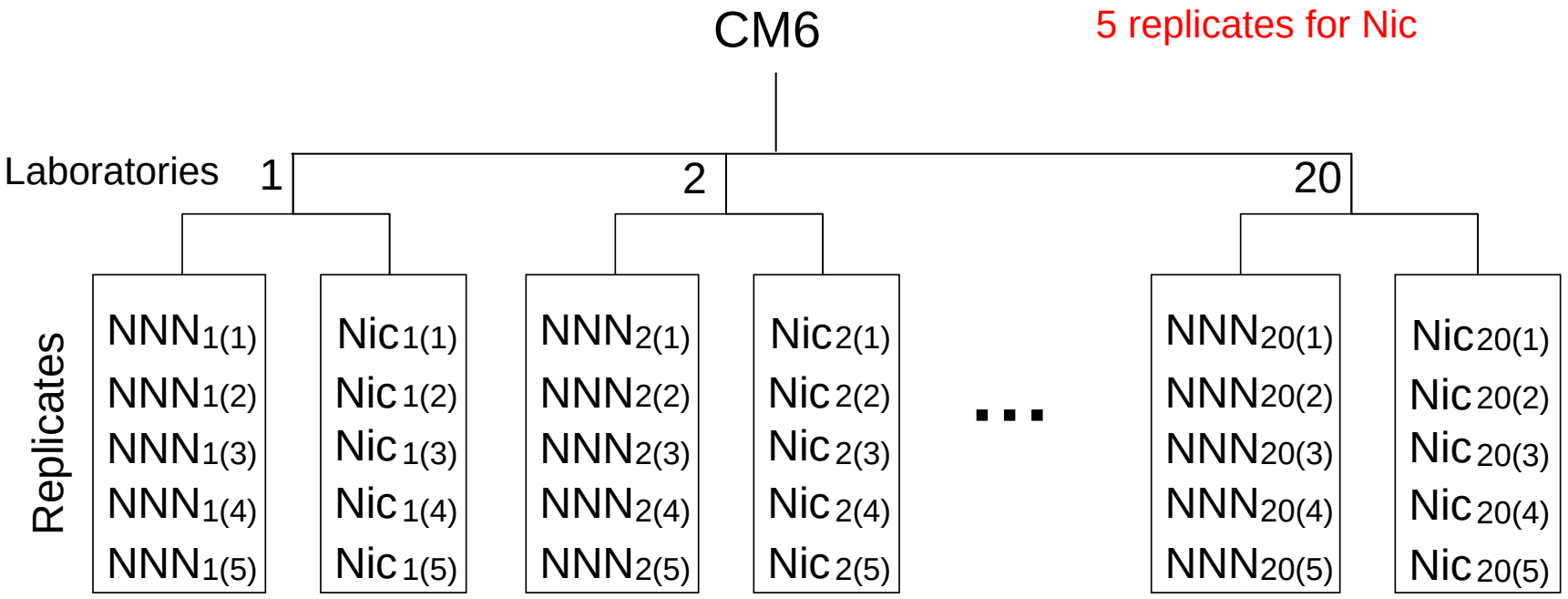
Example:
Collaborative Study (CORESTA)

ratio NNN/Nic

(Unpaired measurements)

20 laboratories (from 1 to 20)
ISO smoking regime

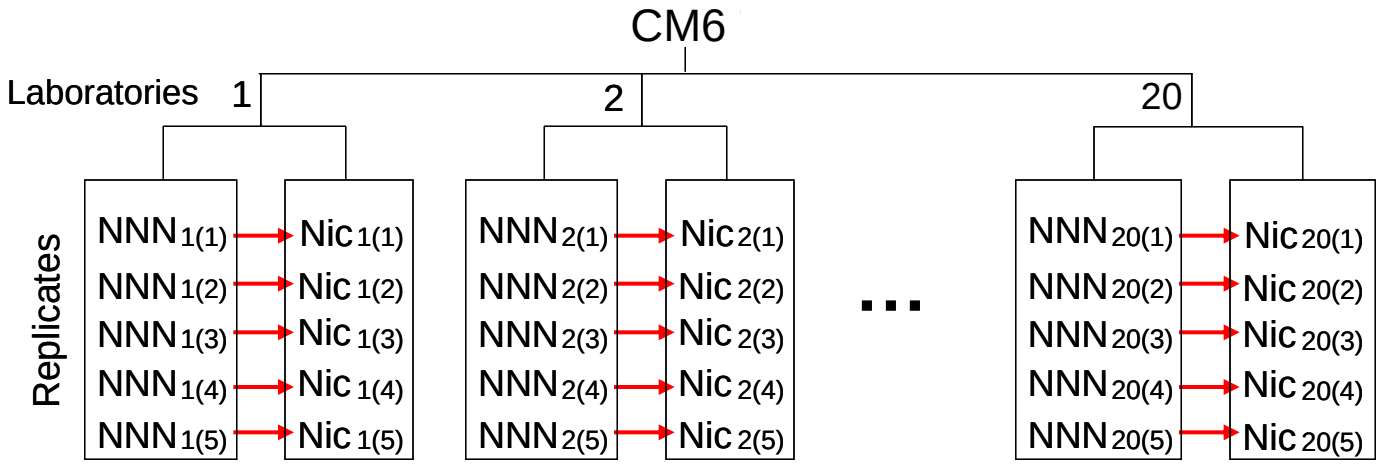
per laboratory:
5 replicates for NNN
5 replicates for Nic



ratio NNN/Nic (Unpaired measurements)

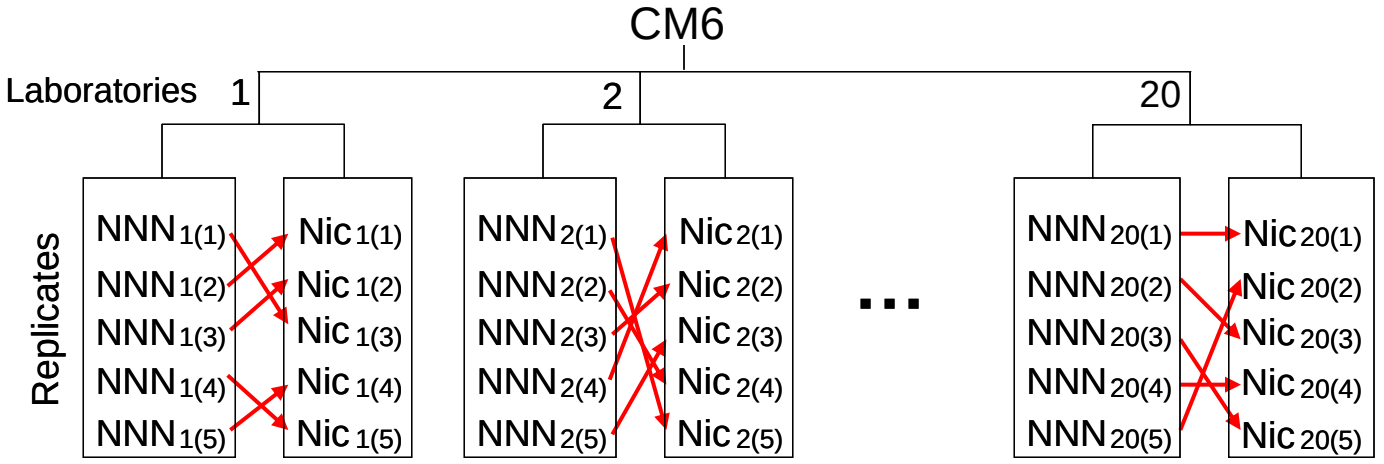
Test 1

R = NNNp(x)/Nic(x)



Test 2

R = NNN/Nic
randomly



ratio NNN/Nic (Unpaired measurements)

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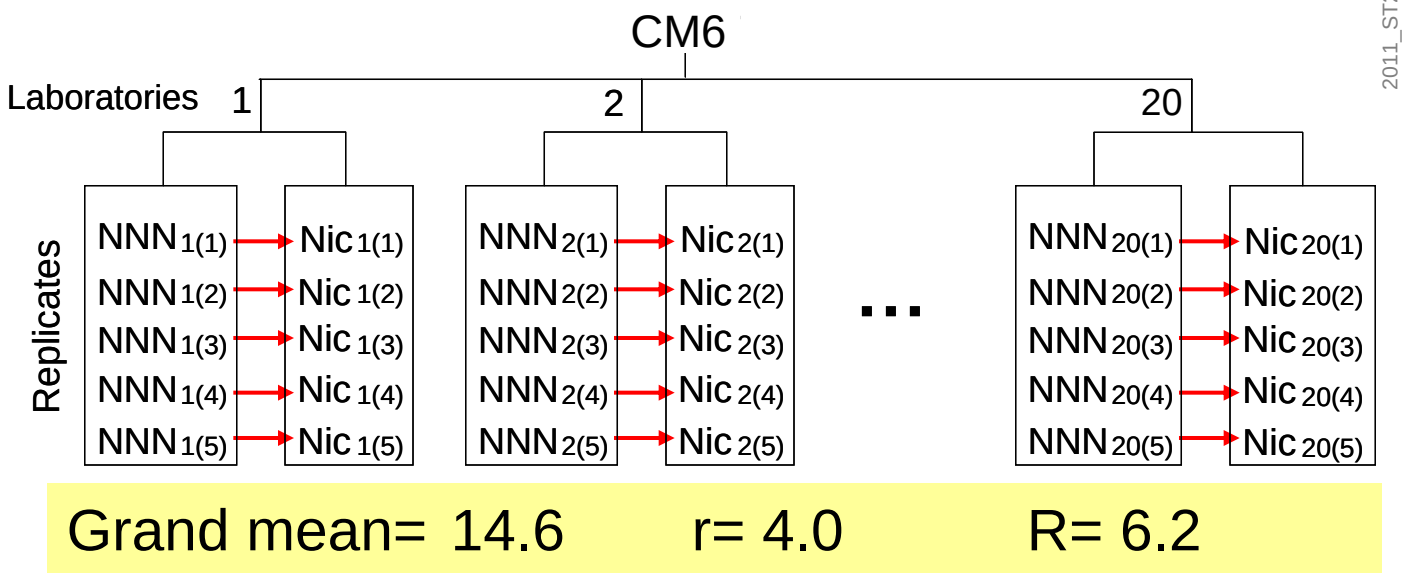
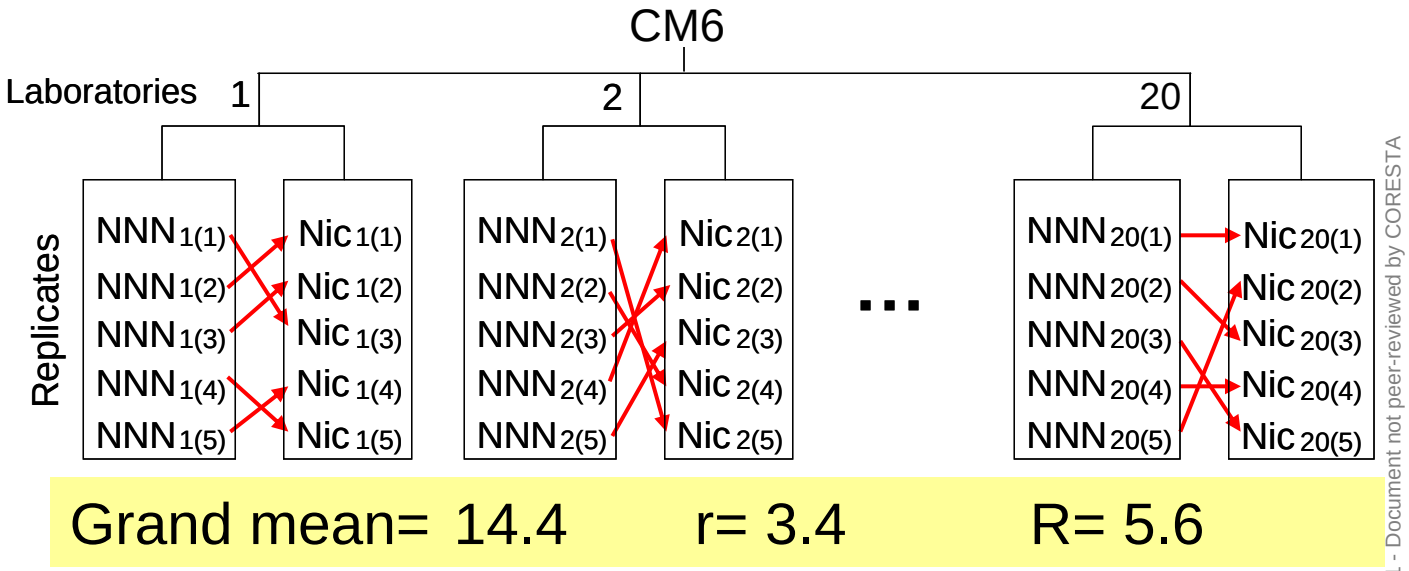


Grand mean= 14.6 r= 4.0 R= 6.2

Test 2

R = NNN/Nic
randomly



Grand mean= 14.4 r= 3.4 R= 5.6

Where is the reality ?

Simulations

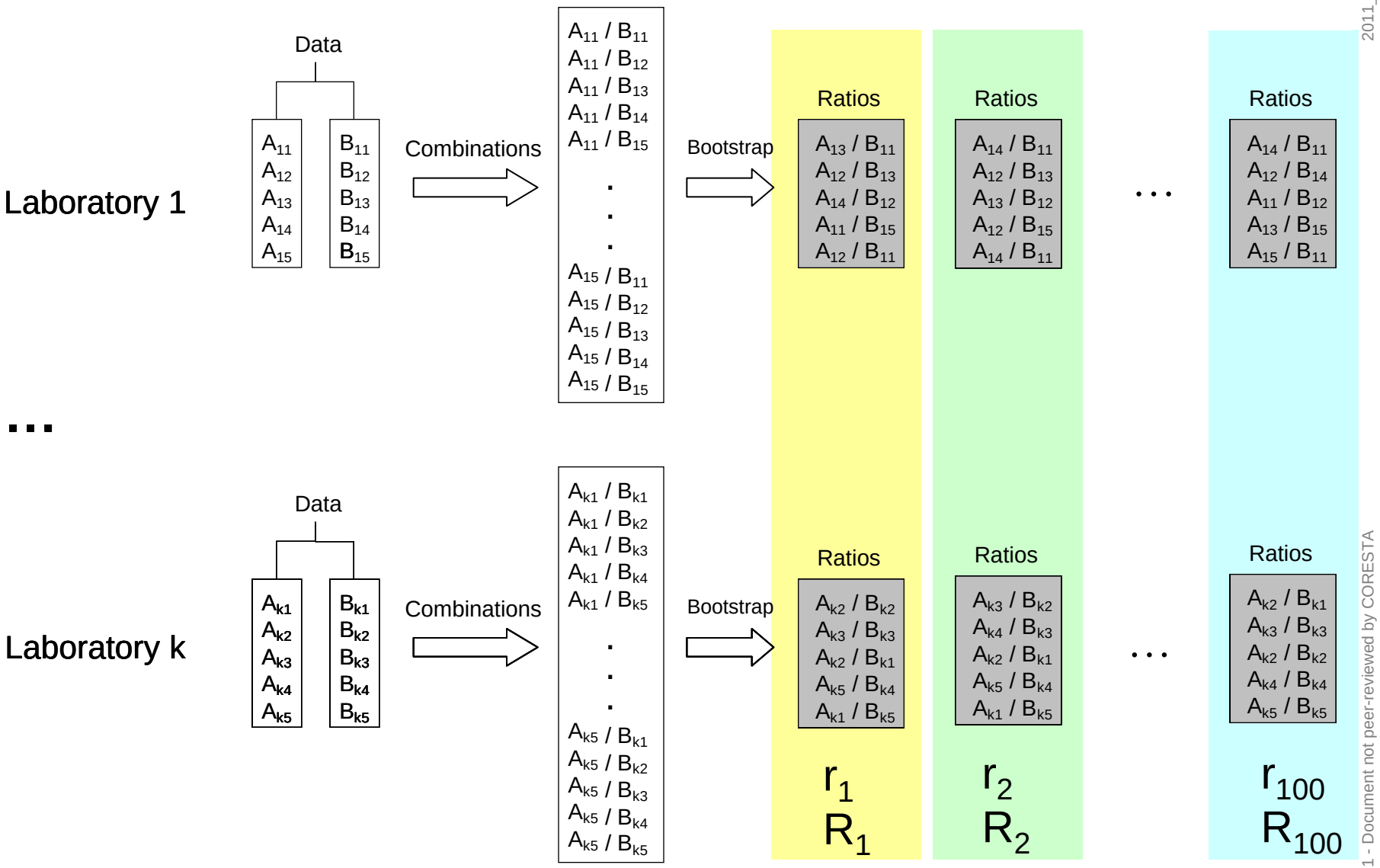
- With only these two chosen tests the repeatability and the reproducibility varied by 36% and 19%, respectively.

- To have an idea of the distribution of the repeatability and reproducibility values, we have made simulations to generate and to evaluate a greater number of tests.

- Simulations are based on “bootstrap” strategies (sampling methodology)

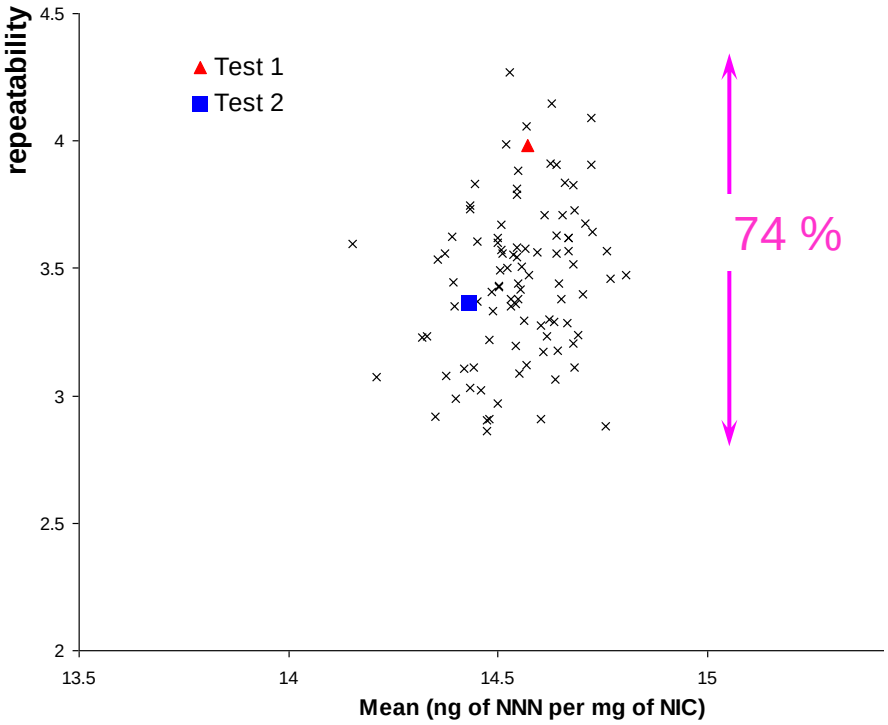
P. M. Dixon, 2002. Bootstrap resampling, Encyclopedia of Environmetrics, 1:212-220.

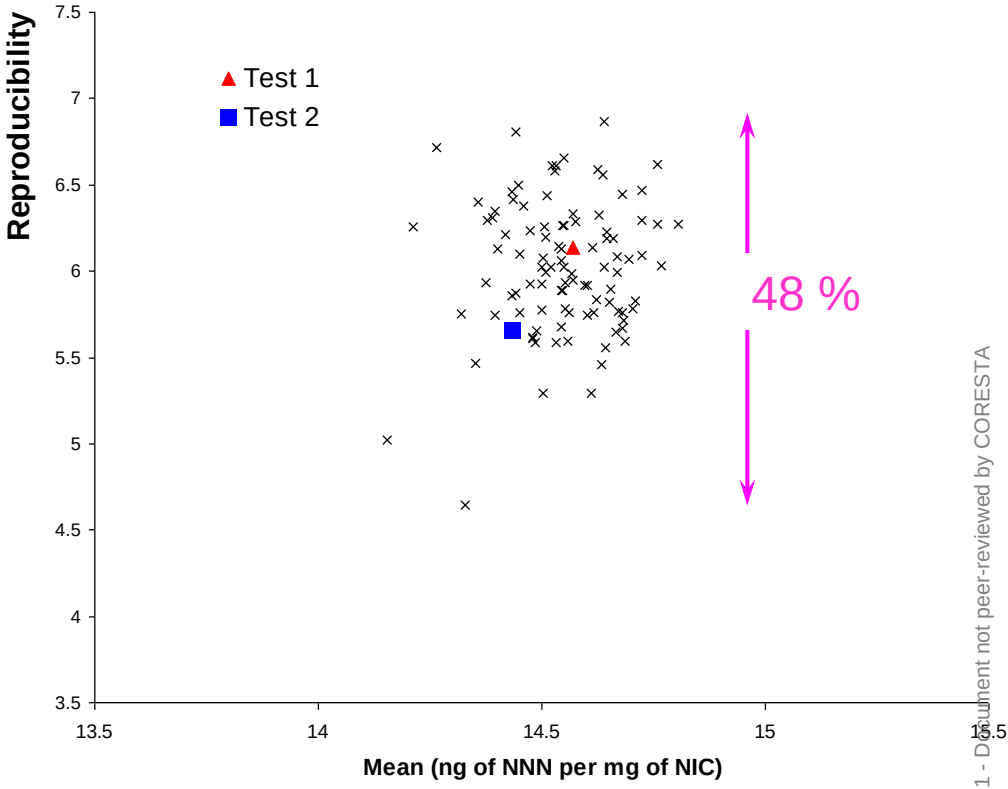
Ratio created by Bootstrap Strategy



Results

CM6
≈ 1.6 mg NIC/cig
≈ 23 ng NNN/cig





ISO smoking method

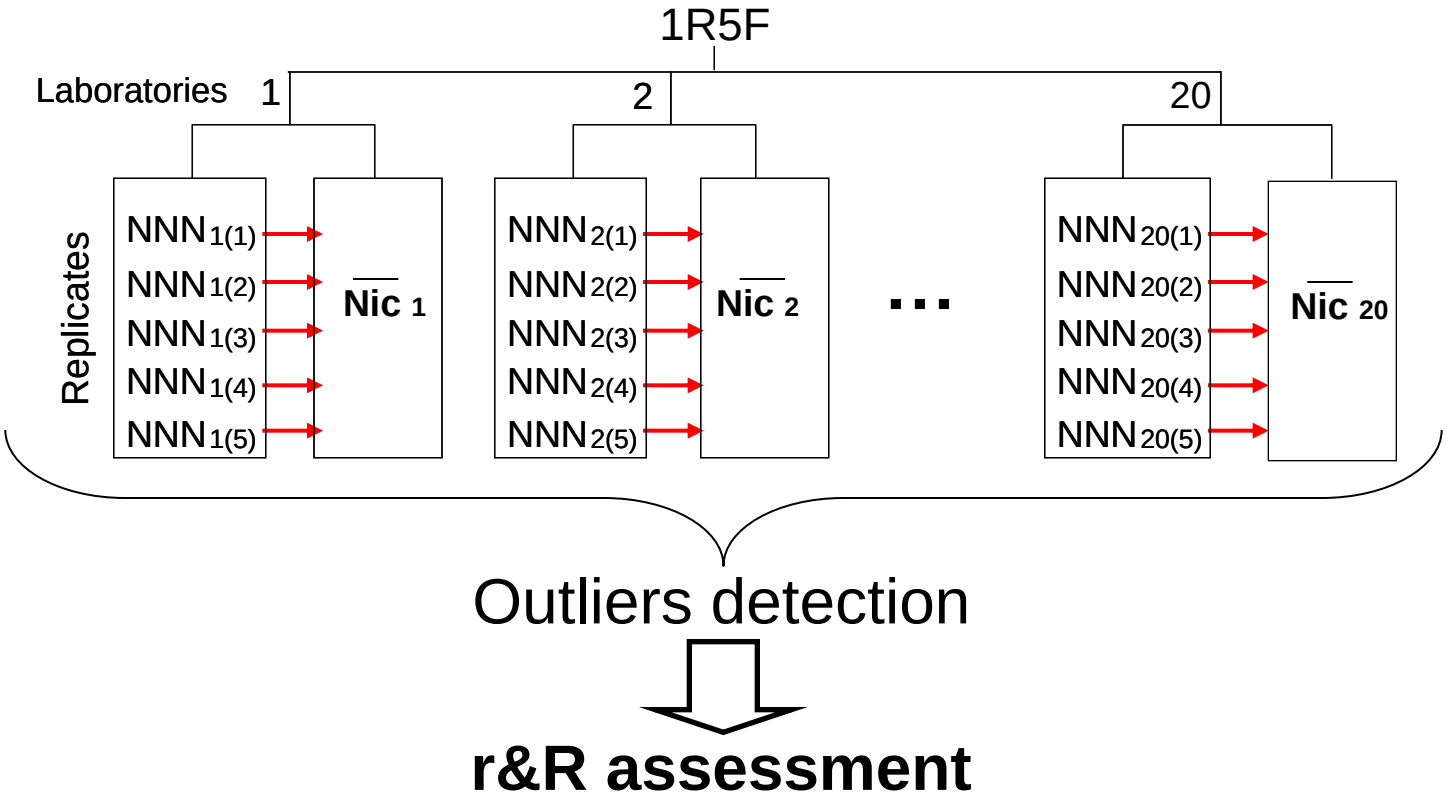
Intermediate conclusion

- Simulations highlighted the wide range of estimated repeatability and reproducibility using nicotine ratio (example NNN/NIC 74% for r and 48% for R).
- **Accuracy of nicotine ratio expression cannot be clearly determined using the basic method for the determination of repeatability and reproducibility defined by ISO 5725 standard.**
- Need to define a strategy to evaluate the r&R or to use alternative approaches.

Alternative approaches

(Ratio mean Nic)

1) Computation of r&R using the mean of nicotine (per laboratory):



- ISO 5725 standard procedure can be applied
- Intra-laboratory standard deviation of nicotine is not taken into consideration (not a problem if the process is under control (ISO))

$$R + \Delta R = \frac{NNN + \Delta NNN}{NIC + \Delta NIC}$$

$$R = \frac{NNN}{NIC}$$

$$R + \Delta R = \frac{NNN(1 + \Delta NNN / NNN)}{NIC(1 + \Delta NIC / NIC)}$$ → *Taylor Expansion*

$$R + \Delta R = \frac{NNN}{NIC}\left(1 + \frac{\Delta NNN}{NNN}\right)\left(1 - \frac{\Delta NIC}{NIC} + \left(\frac{\Delta NIC}{NIC}\right)^2 - \left(\frac{\Delta NIC}{NIC}\right)^3 + \ldots\right)$$

1st hypothesis

If $\frac{\Delta NIC}{NIC}$ small ⇒ $\left(\frac{\Delta NIC}{NIC}\right)^n$ negligible

$$R + \Delta R = \frac{NNN}{NIC}\left(1 + \frac{\Delta NNN}{NNN}\right)\left(1 - \frac{\Delta NIC}{NIC}\right)$$

2nd hypothesis

$$R + \Delta R = \frac{NNN}{NIC}\left(1 + \frac{\Delta NNN}{NNN} - \frac{\Delta NIC}{NIC} - \left(\frac{\Delta NNN}{NNN} \cdot \frac{\Delta NIC}{NIC}\right)\right)$$

If $\frac{\Delta NIC}{NIC}$ and $\frac{\Delta NNN}{NNN}$ small

$$R + \Delta R = \frac{NNN}{NIC} + \frac{NNN}{NIC}\left(\frac{\Delta NNN}{NNN} - \frac{\Delta NIC}{NIC}\right)$$

$$V(\Delta R) = \frac{NNN^2}{NIC^2}\left[\frac{V(\Delta NNN)}{NNN^2} + \frac{V(\Delta NIC)}{NIC^2} - 2\sqrt{V(\Delta NNN) \times V(\Delta NIC)} \times \frac{\rho(\Delta A, \Delta B)}{A \times B}\right]$$

If the measurements are totally unpaired, the **correlation=0**.

3rd hypothesis

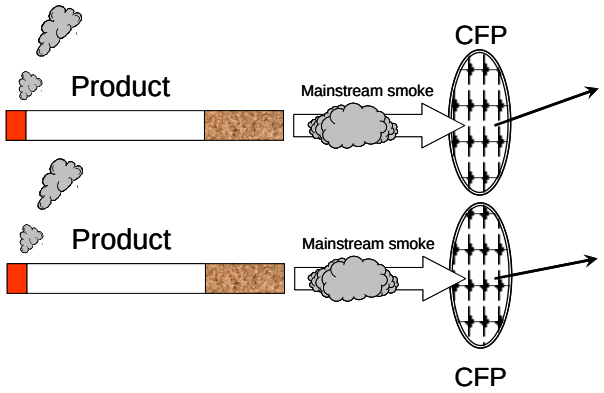
$$V(\Delta R) = \frac{NNN^2}{NIC^2}\left[\frac{V(\Delta NNN)}{NNN^2} + \frac{V(\Delta NIC)}{NIC^2}\right]$$

Alternative approaches

Model EP

2) Theory of Error Propagation:

- Compute the r&R of NNN and NIC using the ISO standard
- Used a **model** to estimate the r&R of the ratio A/NIC



Analyte (A) quantitation ⇨ r_{NNN}&R_{NNN}

Nicotine (B) quantitation ⇨ r_{Nic}&R_{Nic}

Estimation of: $r_{NNN/NIC}$ & $R_{NNN/NIC}$

$$V(\Delta R) = \frac{NNN^2}{NIC^2}\left[\frac{V(\Delta NNN)}{NNN^2} + \frac{V(\Delta NIC)}{NIC^2}\right]$$

- ISO 5725 standard procedure can be applied

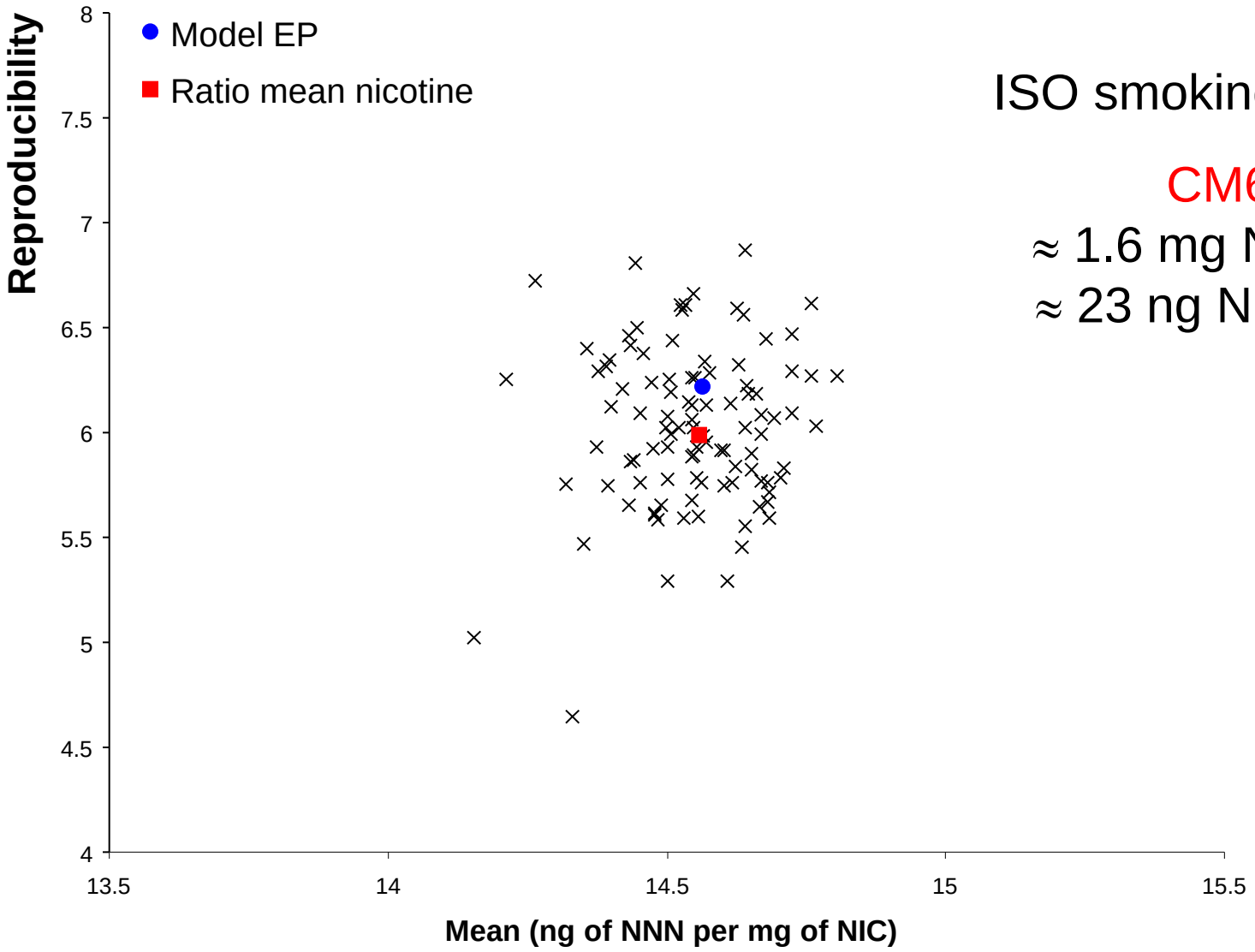
▪The model can only be applied if some hypothesis are true:

1) $\frac{\Delta NIC}{NIC}$ **small** *(Taylor expansion simplification)*

2) $\frac{\Delta NNN}{NNN}$ **small** *(simplification of equations)*

3) **the measurements are totally unpaired, <u>the correlation=0</u>**

Reproducibility



ISO smoking regime

CM6

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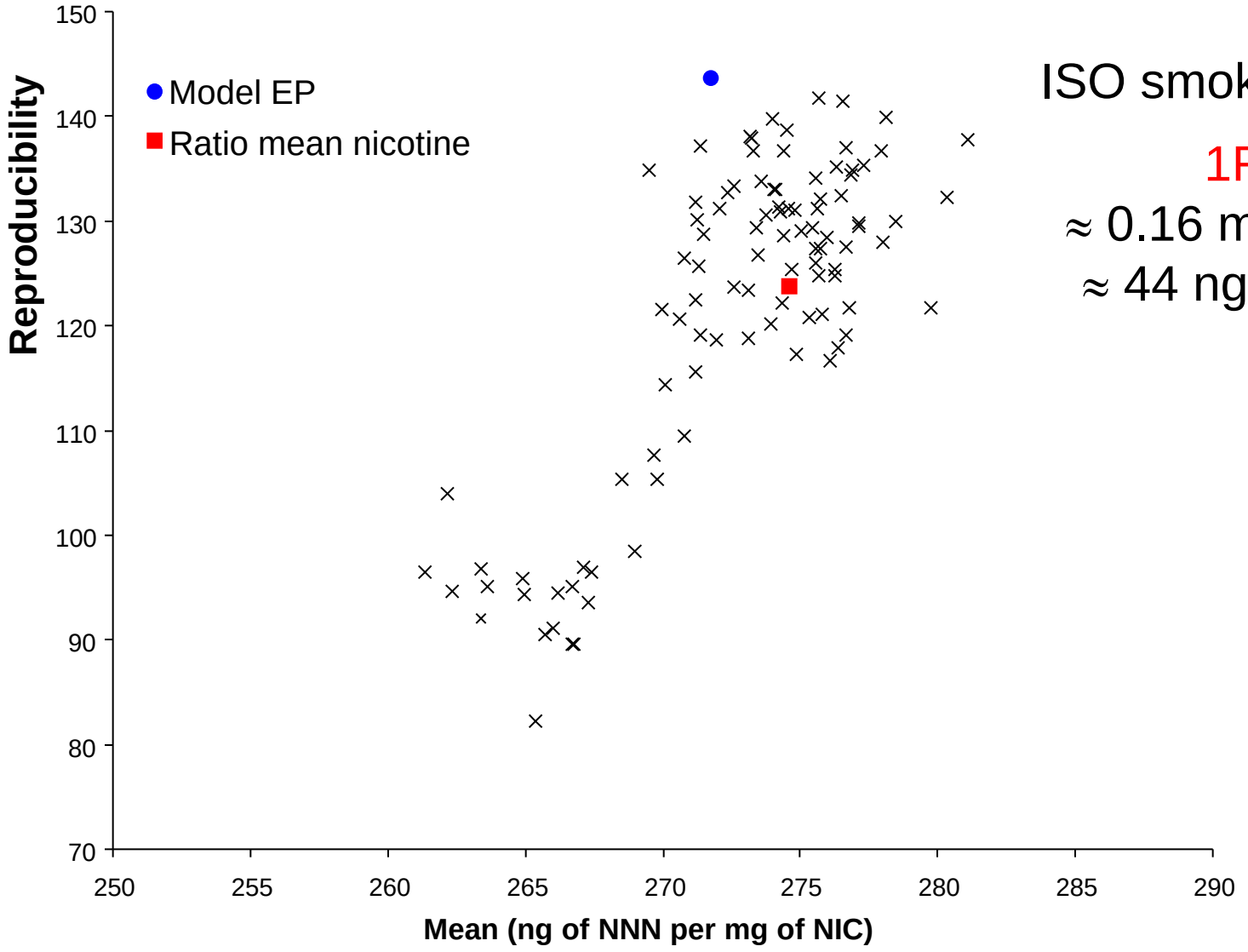
Reproducibility



ISO smoking regime

1R5F

≈ 0.16 mg NIC/cig

≈ 44 ng NNN/cig

Conclusions

- The best method to determine r&R using nicotine ratio is to perform paired measurements
- Some alternative approaches can be suggested. However, each proposal has drawbacks
- The different approaches can give different results of r&R, especially for low nicotine yield cigarettes
- Further investigations are under progress to know which alternative approaches (Model EP or Nic mean) could fit the purpose