COMPARISON OF STATISTICAL AND MATHEMATICAL METHODS IN SUPPORT OF EQUIVALANCE TESTING

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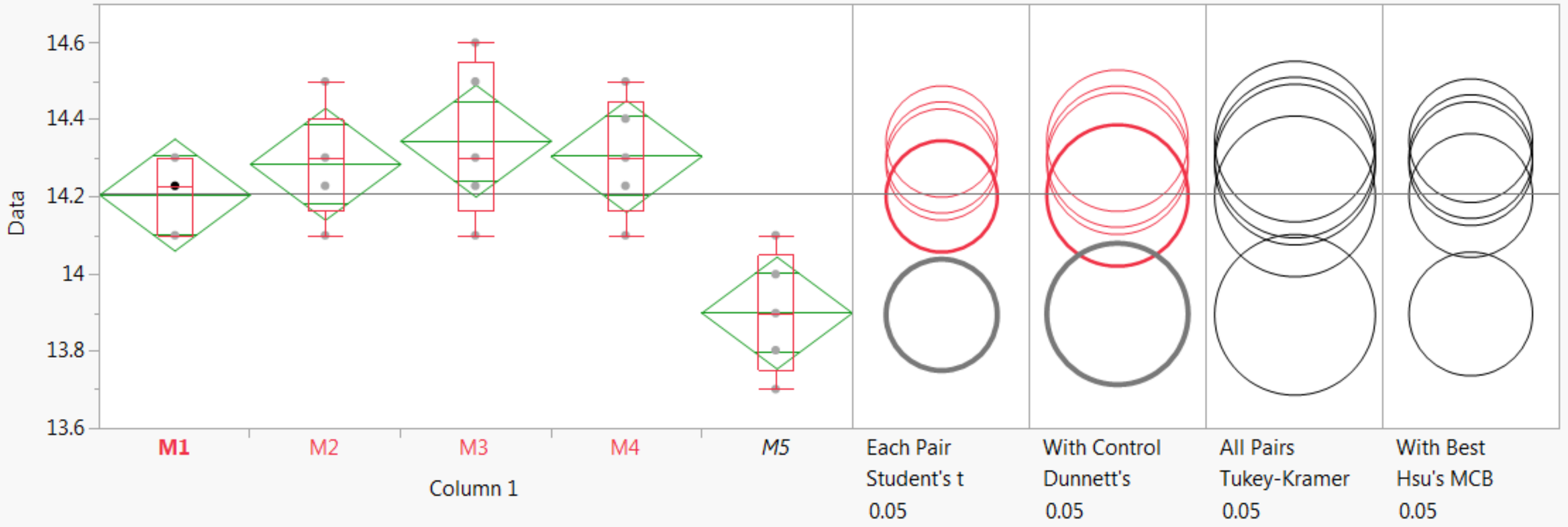
Untitled 6 - Fit Y by X of Data by Column 1 - JMP

Oneway Analysis of Data By Column 1



Where the *t*-test Fails

- Precision is very good
- Precision is poor
- n is small

- Hypothesis is that the means are similar

Hypothesis Testing

- X is Different
  - Control versus purposeful change
  - Suspect value
  - Student's *t*-test, ANOVA

- X is Equivalent/Not Different
  - Process scale-up
  - Methods transfer
  - Equivalent materials substitution
  - Batch to batch comparisons

Potential Real World Cigarette Applications

- Testing of the same batch at different labs
  - Insights from initial analysis for harmful and potentially harmful constituents (HPHC)…CORESTA 2013 ST#23

- Testing of multiple batches of the same products
  - Variation in toxicant yields from selected products… CORESTA 2013 IG#02
  - Multiple point in time evaluation of commercial and reference cigarette products …CORESTA 2013 ST#59
  - In progress CVAR study to understand product variability

Techniques Explored

- Percent Difference & Visual Inspection
- Repeatability & Reproducibility
- Critical Difference
- Confidence Interval Analysis
- Two One-Sided t-Test (TOST)

Percent Difference & Visual Inspection

- Percent difference, percent error, relative difference* depending on design
- Quick and simple way to assess a range of data

- Requires experience/knowledge: methods, measures, study design, sample type

Percent difference = (2*(A-B))/(A+B)*100; two samples, assumes no control
Percent error = (A-B)/A*100; two samples, assumes A is the control
Relative Percent difference = (2*(max-min))/(max+min); >two samples, assumes no control

% Difference

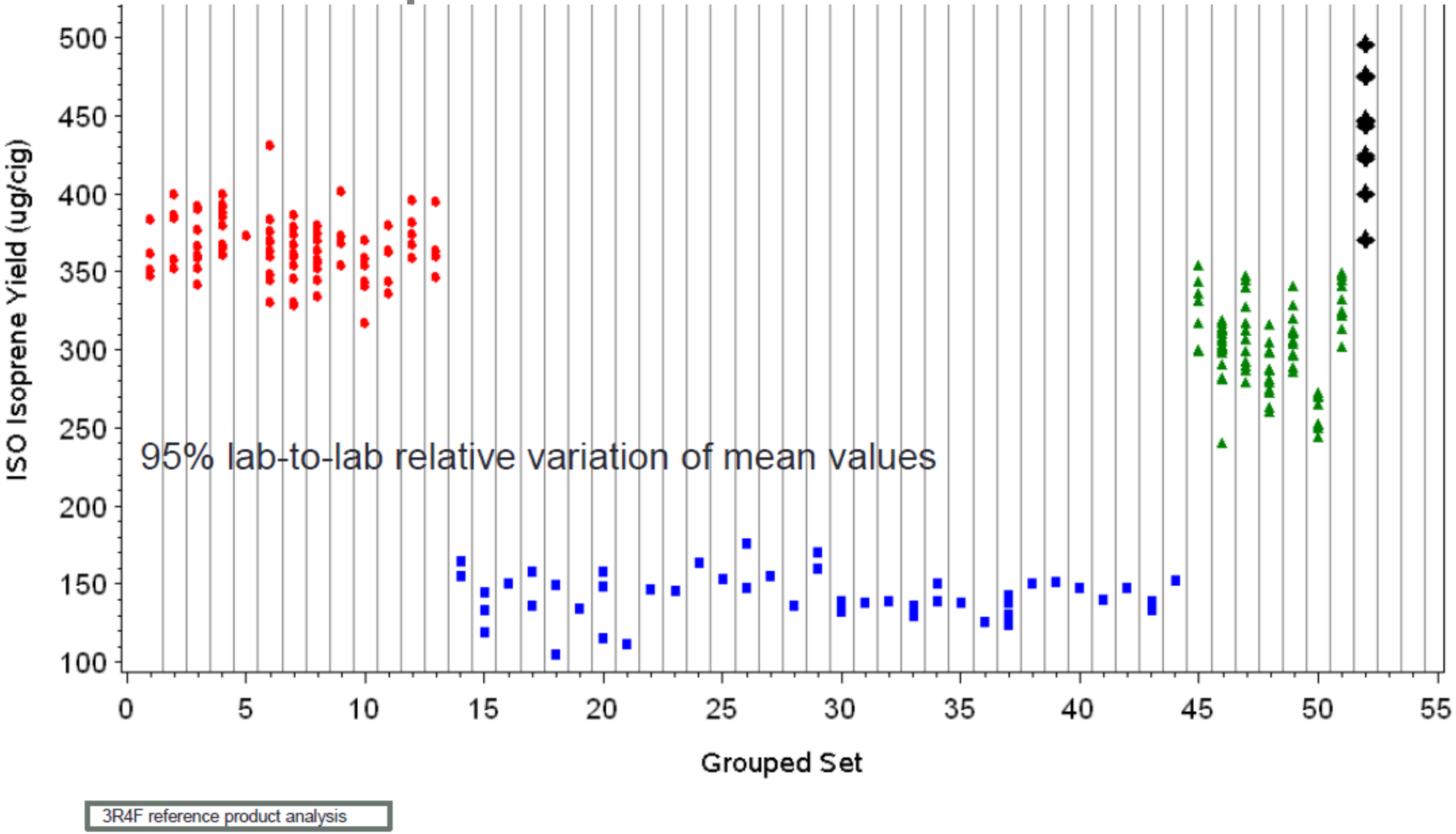
Analyte		Lab A	Lab B	Lab C	Lab D	Relative Difference
Carbon Monoxide	mg/cig	10.2	10.2	10.3	11.3	10%
Nicotine	mg/cig	0.66	0.68	0.71	0.68	6%
Formaldehyde	µg/cig	25.1	24.8	20.1	13.0	64%*
Acrolein	µg/cig	53.3	52.1	45.9	58.7	24%
NNK	ng/cig	91.7	99.7	98.7	99.4	8%
1-Aminonaphthalene	ng/cig	14.5	14.3	12.7	10.4	32%

Mainstream Smoke yields for 3R4F cigarettes, ISO
Methods were not necessarily the same for the different labs

*22% if Lab D not considered

Adapted from: Harmful and Potentially Harmful Constituents Analysis and Considerations, Industry Presentation to the Center for Tobacco Products February 14, 2013

Visual Inspection



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Repeatability & Reproducibility

- Comparisons to limit values
- Good for well-established methods (TNCO)
- Applicable to most any method
- Less limited by need for experience with system

- Requires experimentation with in-common methods
- Scope of application across products may depend on study design

ISO 5725

Repeatability & Reproducibility

Mean value m_{NFDPM}	Repeatability limit r	Reproducibility limit R
0.82	0.40	0.60
1.61	0.52	0.74
3.31	0.52	0.90
7.70	0.88	1.51
12.61	1.06	1.70
17.40	1.19	1.84

ISO_4387-2000 Cigarettes — Determination of total and nicotine-free dry particulate matter using a routine analytical smoking machine; calculated to expect fewer than 1 in 20 random fails

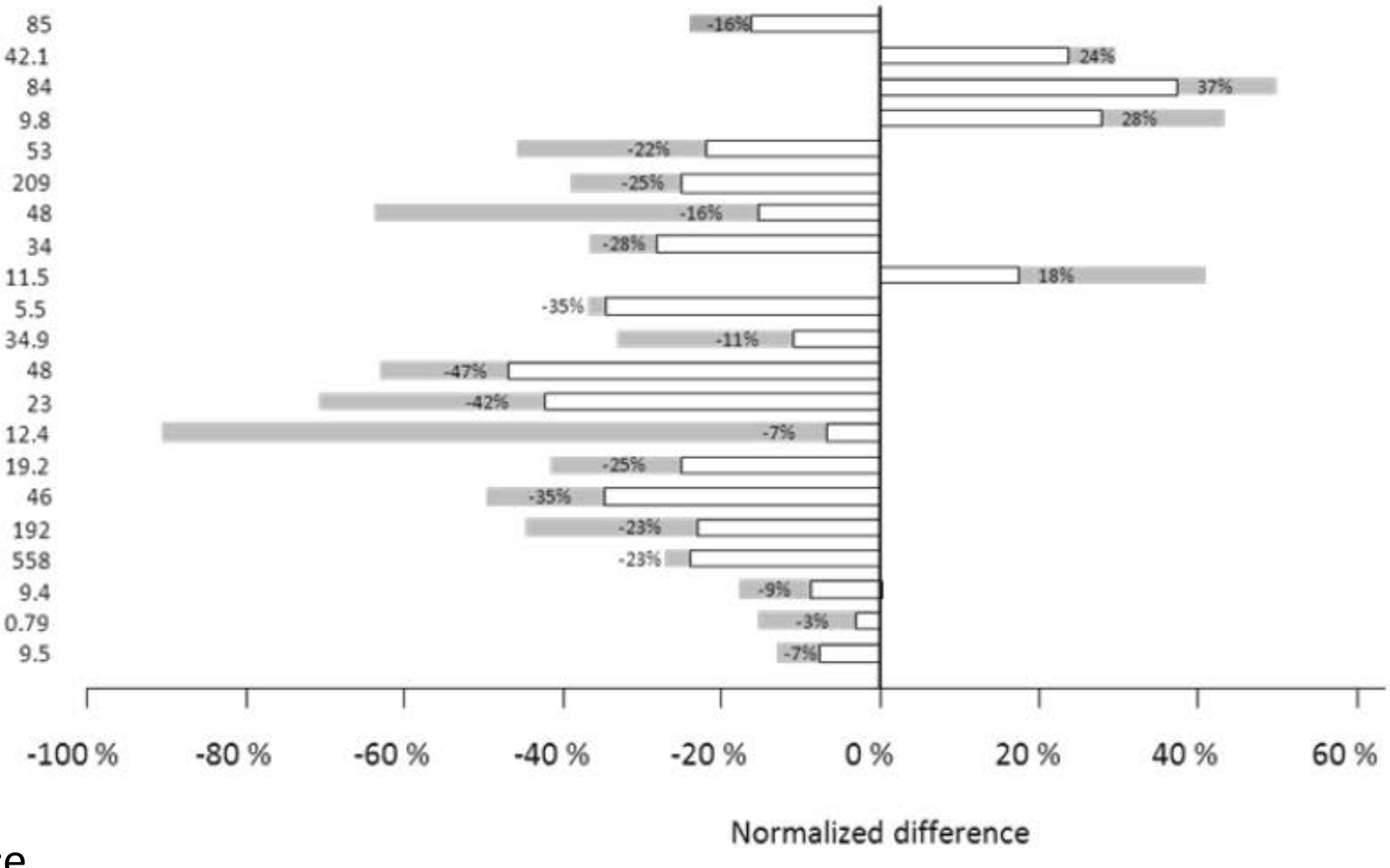
Critical Difference

- Maximum difference expected between two final values with a specified probability
- Calculated from r&R values and intermediate precision
- Compare actual difference to CD

ISO_5725 part 6

Critical Difference

	Brand 1 Lab A	Brand 1 Lab B
NNN	100	85
NNK	33.1	42.1
NAT	58	84
NAB	7.4	9.8
Toluene	66	53
Isoprene	345	209
Butadiene	56	48
Benzene	45	34
Acrylonitrile	9.6	11.5
Benzo[a]pyrene	7.9	5.5
Propionaldehyde	38.9	34.9
Methyl ethyl keton	77	48
Formaldehyde	36	23
Crotonaldehyde	13.3	12.4
Butyraldehyde	24.7	19.2
Acrolein	65	46
Acetone	242	192
Acetaldehyde	716	558
CO	10.3	9.4
NICO	0.81	0.79
TAR	10.2	9.5



Gray = CD value

White = actual difference

B. Teillet, X. Cahours, T. Verron, S. Colard, S. Purkis. Comparison of Smoke Yield Data Collected from Different Laboratories. Beitr. Tabakforsch. Int. 25 (2013) 663-670.

Confidence Interval Analysis

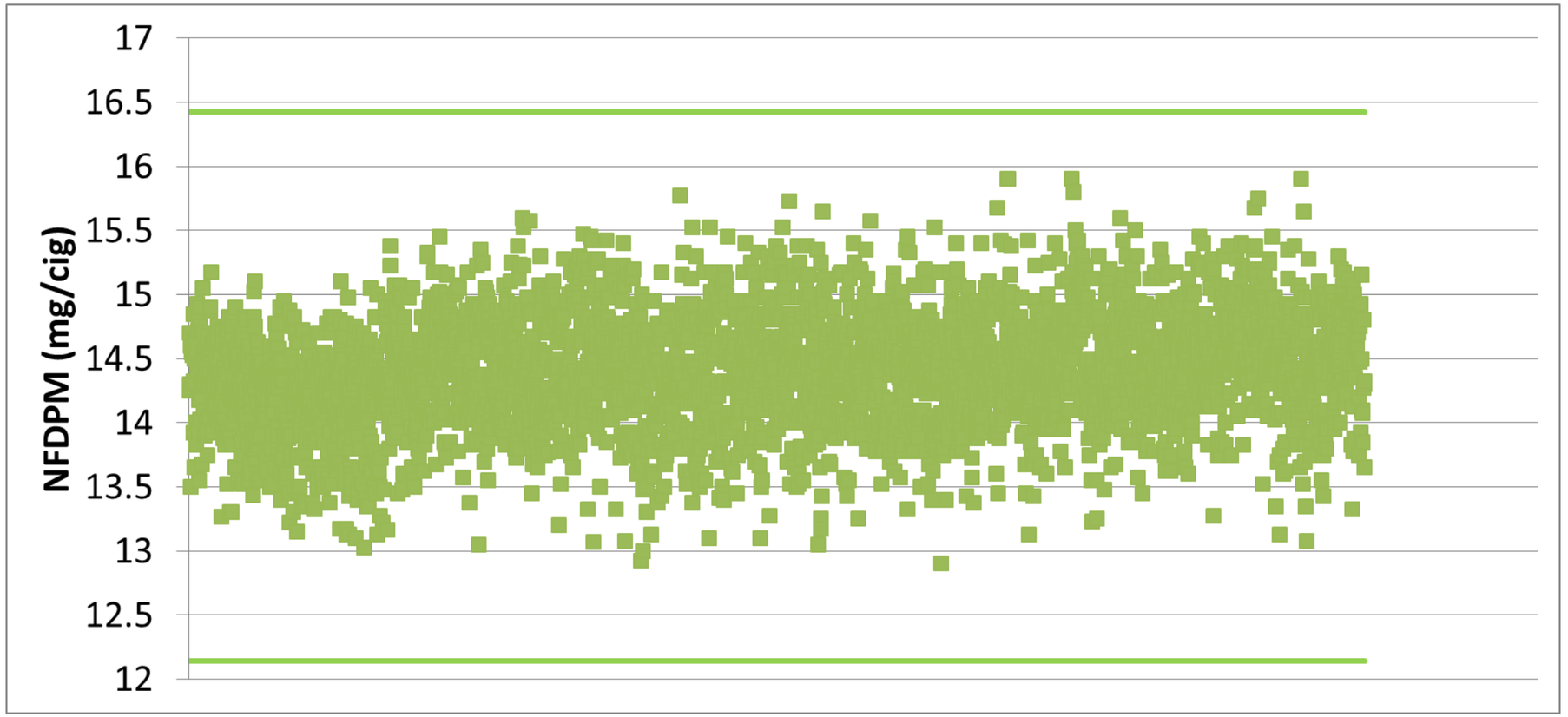
Table 3 — Confidence interval

Smoke constituent and ISO measurement method	Sampling	
	Over a period of time (Clause 5)	At one point in time (4.1 and 4.2)
NFDPM (ISO 4387 and ISO 10362-1)	± 15 %	± 20 %
Nicotine (ISO 10315)	± 15 %	± 20 %
Carbon monoxide (ISO 8454)	± 20 %	± 25 %
NOTE These confidence intervals will not be smaller than ± 1 mg for NFDPM, ± 1,5 mg for CO and ± 0,1 mg for nicotine.		

*Calculated with a target that on average no more than 1 in 20 determinations are likely to be outside of the interval purely by chance.; not calculated in accordance with ISO 2602

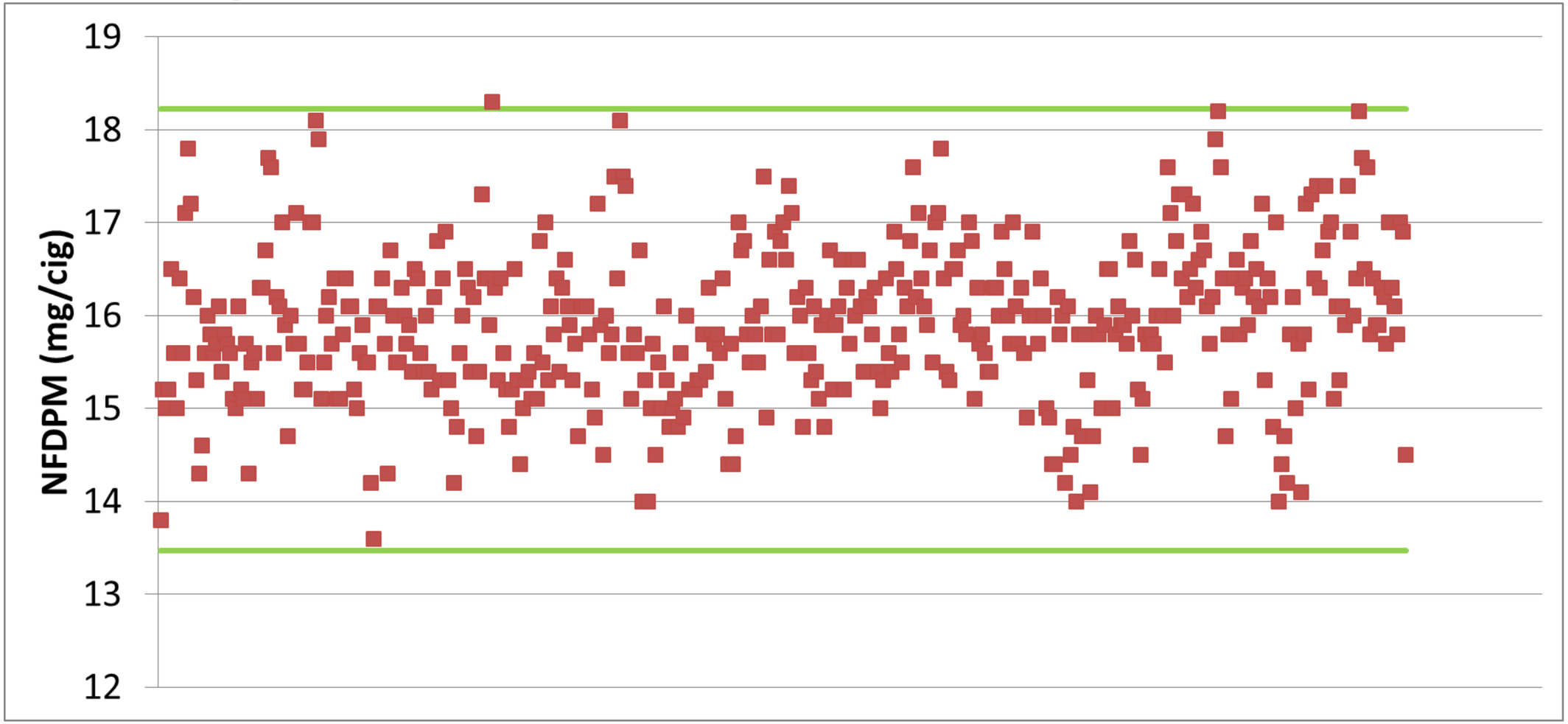
ISO 8243-2013 Cigarettes – Sampling

Confidence Interval Analysis – Repeat Testing over time



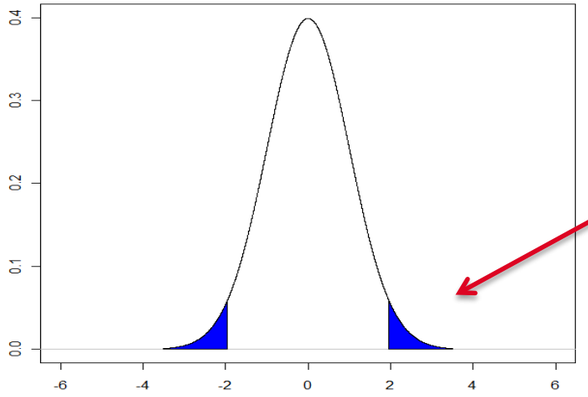
n=3488, 15% long term CI limits

Confidence Interval Analysis – Batch to Batch Comparisons over time

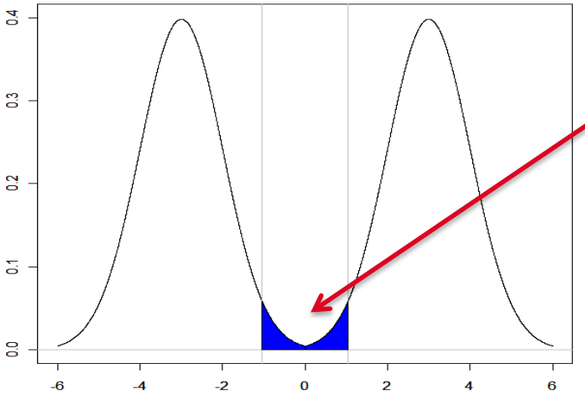


n=451, 15% long term CI limits

Two one-sided t-test (TOST)

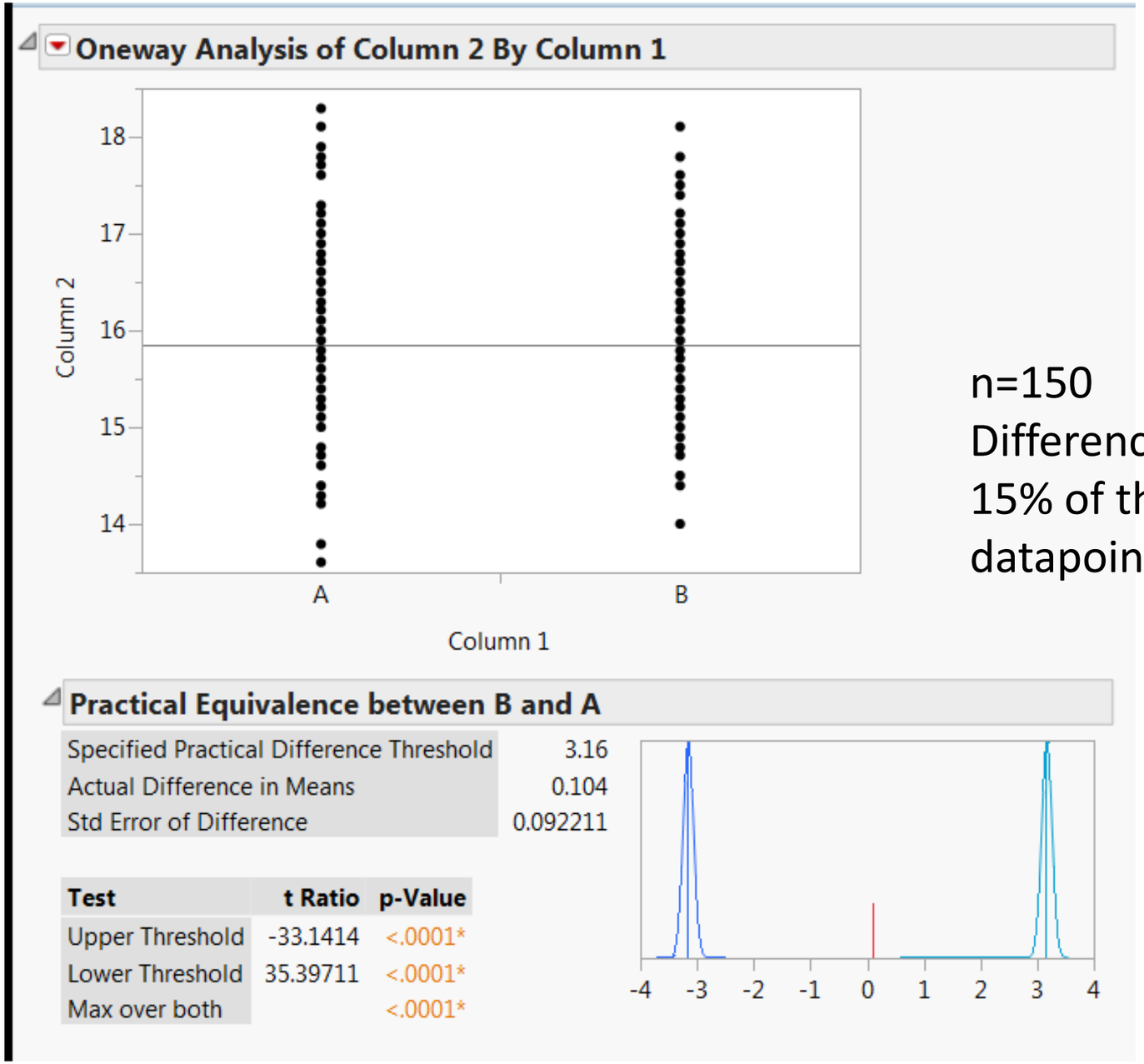


Two sample t-test



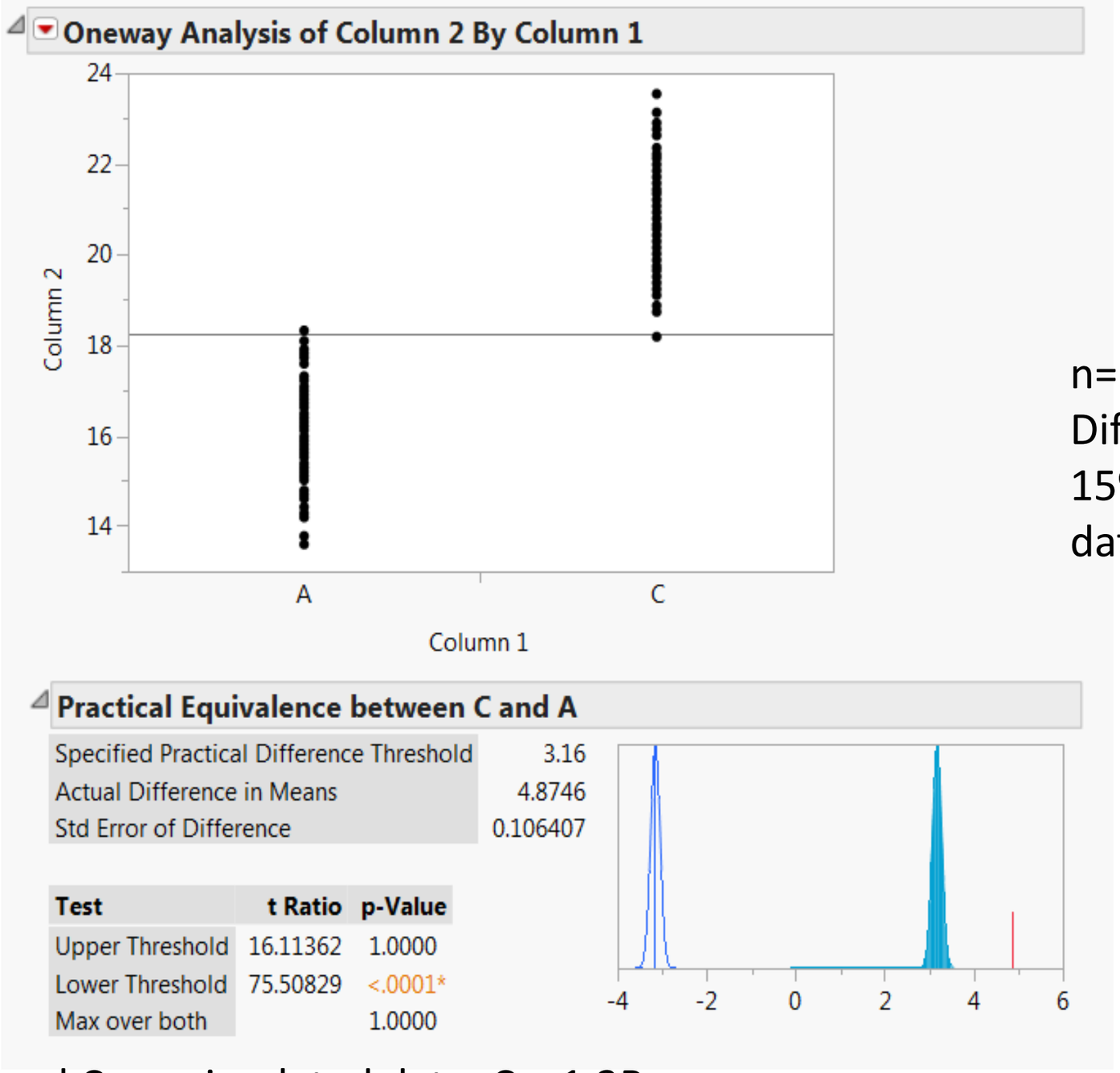
Two one sample t-test

If the difference between means falls in this range, we would conclude the means belong to equivalent groups/are not substantially different.



n=150
Difference threshold = 3.16 as 15% of the avg of 1089 datapoints of a control

Where A and B are simulated data



n=150
Difference threshold = 3.16 as 15% of the avg of 1089 datapoints of a control

Where A and C are simulated data; C = 1.3B

Conclusions

- There are several options available for evaluating data expected to be similar/equivalent

- r&R, Critical Difference, Confidence Intervals
  - Require in-common methods
  - Establishment through experimentation
  - Straightforward calculations against limits

- % Difference, TOST
  - Require experience
  - Require systemic knowledge

References

- ISO_5725 Set
- ISO_4387-2000 Cigarettes — Determination of total and nicotine-free dry particulate matter using a routine analytical smoking machine
- ISO 8243-2013 Cigarettes – Sampling
- Eldridge A.; Betson T.; McAdam K. Variation in toxicant yields from selected products CORESTA Meeting Smoke Sci.-Prod. Techno Groups, Seville, 2013, abstr. IG 02
- Tayyarah, R. Multiple point in time evaluation of commercial and reference cigarette products for abbreviated HPHC yield for mainstream smoke and filler CORESTA Meeting Smoke Sci.-Prod. Techno Groups, Seville, 2013, abstr. ST 59
- Wagner K.A.; Desoi D.; Morton M.J.; Oldham M.J. Insights from initial analysis for harmful and potentially harmful constituents (HPHC) in cigarette and smokeless tobacco products CORESTA Meeting Smoke Sci.-Prod. Techno Groups, Seville, 2013, abstr. ST 23
- Harmful and Potentially Harmful Constituents Analysis and Considerations, Industry Presentation to the Center for Tobacco Products February 14, 2013
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- B. Teillet, X. Cahours, T. Verron, S. Colard, S. Purkis. Comparison of Smoke Yield Data Collected from Different Laboratories. Beitr. Tabakforsch. Int. 25 (2013) 663-670.
- Limentani, G. *et al.* Beyond the t-Test: Statistical Equivalence Testing, Analytical Chemistry June 2005.