RESEARCH & DEVELOPMENT

Multiple point in time evaluation of commercial and reference cigarette products for abbreviated HPHC yield for mainstream smoke and filler

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Topics

- Background
- Experimental Design
- Reference Products
- Commercial Products
- Key Findings
- Conclusions

US Statutory Requirements

2009 Family Smoking Prevention and Tobacco Control Act

- Section 904(e) of the Act requires FDA to establish no later than April 2012 a list of all constituents identified by FDA as harmful or potentially harmful (HPHCs) in tobacco products and tobacco smoke.

- Section 915 of the Act requires FDA to promulgate, no later than April 2013, regulations governing the "testing and reporting of. . . smoke constituents, by brand and subbrands that [FDA] determines should be tested to protect the public health."

- Section 904(d)(1) of the Act requires FDA to publish the list of harmful and potentially harmful constituents in tobacco products in a format that is "understandable and not misleading to a lay person . . ."

February 2013 Presentation to the FDA[1]

- Lab-to-lab data comparison for 3R4F (single batch reference)
- ISO and CI smoking and filler HPHC analytes
- >20% differences in means for many analytes
- >>20% for some analytes
- Variability was generally lower for analytes in higher concentrations (mg<ng)
- Variability was generally lower where standardized methods were employed

Experimental Design

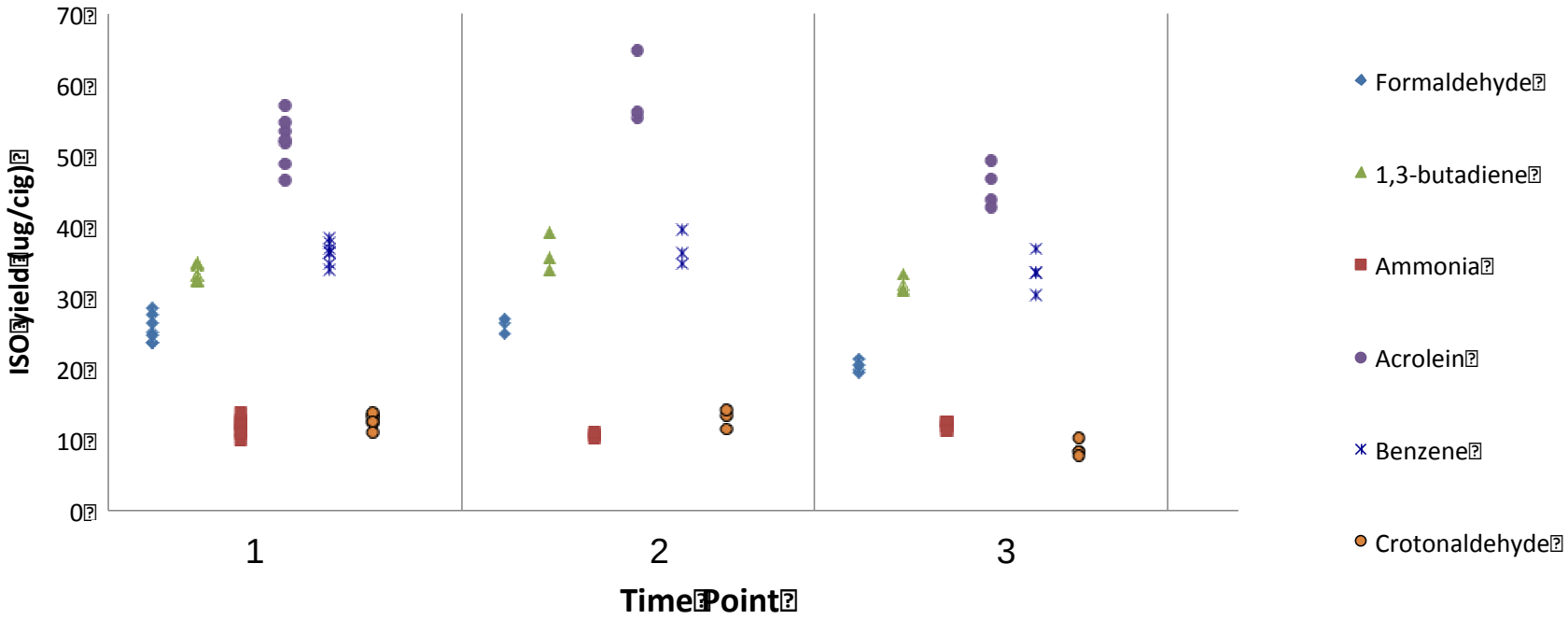
- Commercial cigarette products, 3 time points
- Testing within ~2months after making for each batch
- 3R4F, 1R5F, CM6, concurrent testing, as samples (not monitors)
- FDA's abbreviated HPHC list[2]
- Temporal variability versus batch to batch variability
- Average, standard deviation, % Difference (range)
- Statistical testing – equivalence testing may be warranted for long-term product evaluations

Temporal Variability – ISO 3R4F

	T1	T2	T3	Difference
CO (mg/cig)	10.1 ± 0.5	10.4 ± 0.5	9.7 ± 0.8	**7%**
Nicotine (mg/cig)	0.66 ± 0.03	0.71 ± 0.02	0.67 ± 0.04	**7%**
Ammonia (µg/cig)	11.9 ± 1.2	10.7 ± 0.4	12.1 ± 0.6	**12%**
Formaldehyde (µg/cig)	25.7 ± 1.9	26.1 ± 1.1	20.3 ± 0.9	**25%**
Acetaldehyde (µg/cig)	466 ± 32	510 ± 39	395 ± 27	**25%**
Acrolein (µg/cig)	52.1 ± 3.5	58.8 ± 5.2	45.7 ± 2.9	**41%**
Crotonaldehyde (µg/cig)	12.8 ± 0.9	13.0 ± 1.3	8.6 ± 1.1	**25%**
1,3-butadiene (µg/cig)	33.6 ± 1.1	36.2 ± 2.7	31.9 ± 1.0	**13%**
Isoprene (µg/cig)	305 ± 13	310 ± 26	284 ± 8	**11%**
Acrylonitrile (µg/cig)	7.4 ± 0.5	7.6 ± 0.7	6.8 ± 0.5	**9%**
Benzene (µg/cig)	36.4 ± 1.5	36.9 ± 2.4	33.6 ± 2.6	**9%**
Toluene (µg/cig)	61.3 ± 4.8	59.2 ± 5.2	57.1 ± 4.8	**7%**
Benzo(a)pyrene (ng/cig)	5.4 ± 0.4	6.6 ± 0.1	6.6 ± 0.1	**21%**
1-amino-naphthalene (ng/cig)	15.0 ± 1.0	13.3 ± 0.6	14.2 ± 1.3	**12%**
2-amino-naphthalene (ng/cig)	10.9 ± 1.2	8.8 ± 0.5	9.5 ± 0.6	**21%**
4-amino-biphenyl (ng/cig)	1.48 ± 0.12	1.40 ± 0.10	1.41 ± 0.04	**5%**
NNN (ng/cig)	114 ± 6	112 ± 2	111 ± 4	**3%**
NNK (ng/cig)	98.4 ± 5.4	102 ± 1	95.5 ± 3.4	**7%**

average±1 standard deviation, n=3-7; %Difference between min and max averaged value

Temporal Variability – ISO 3R4F



Temporal Variability – ISO Smoking References

	3R4F	1R5F	CM6
Nicotine (mg/cig)	7%	17%	9%
CO (mg/cig)	7%	31%	4%
Ammonia (µg/cig)	12%	27%	7%
Carbonyls (µg/cig)	25% – 41%	10% – 19%	13% – 22%
VOCs (µg/cig)	7% – 13%	4% – 34%	2% – 13%
PAA (ng/cig)	5% – 21%	6% – 21%	13% – 32%
BaP (ng/cig)	21%	18%	19%
TSNA (ng/cig)	3% – 7%	15% – 19%	5% – 14%

Batch To Batch Variability – ISO Smoking Products

	Product A	Product B	Product C
Nicotine (mg/cig)	4%	4%	10%
CO (mg/cig)	8%	12%	23%
Ammonia (µg/cig)	17%	19%	23%
Carbonyls (µg/cig)	10% - 17%	9% - 19%	13% - 31%
VOCs (µg/cig)	2% - 14%	8% - 20%	4% - 28%
PAA (ng/cig)	8% - 25%	2% – 32%	4% - 22%
BaP (ng/cig)	8%	18%	20%
TSNA (ng/cig)	49% - 56%	31% – 37%	30% - 58%

TSNA % Difference ranged from 11% - 61% for all brands sampled; averaged ~35%

Batch To Batch Variability – CI Smoking Products

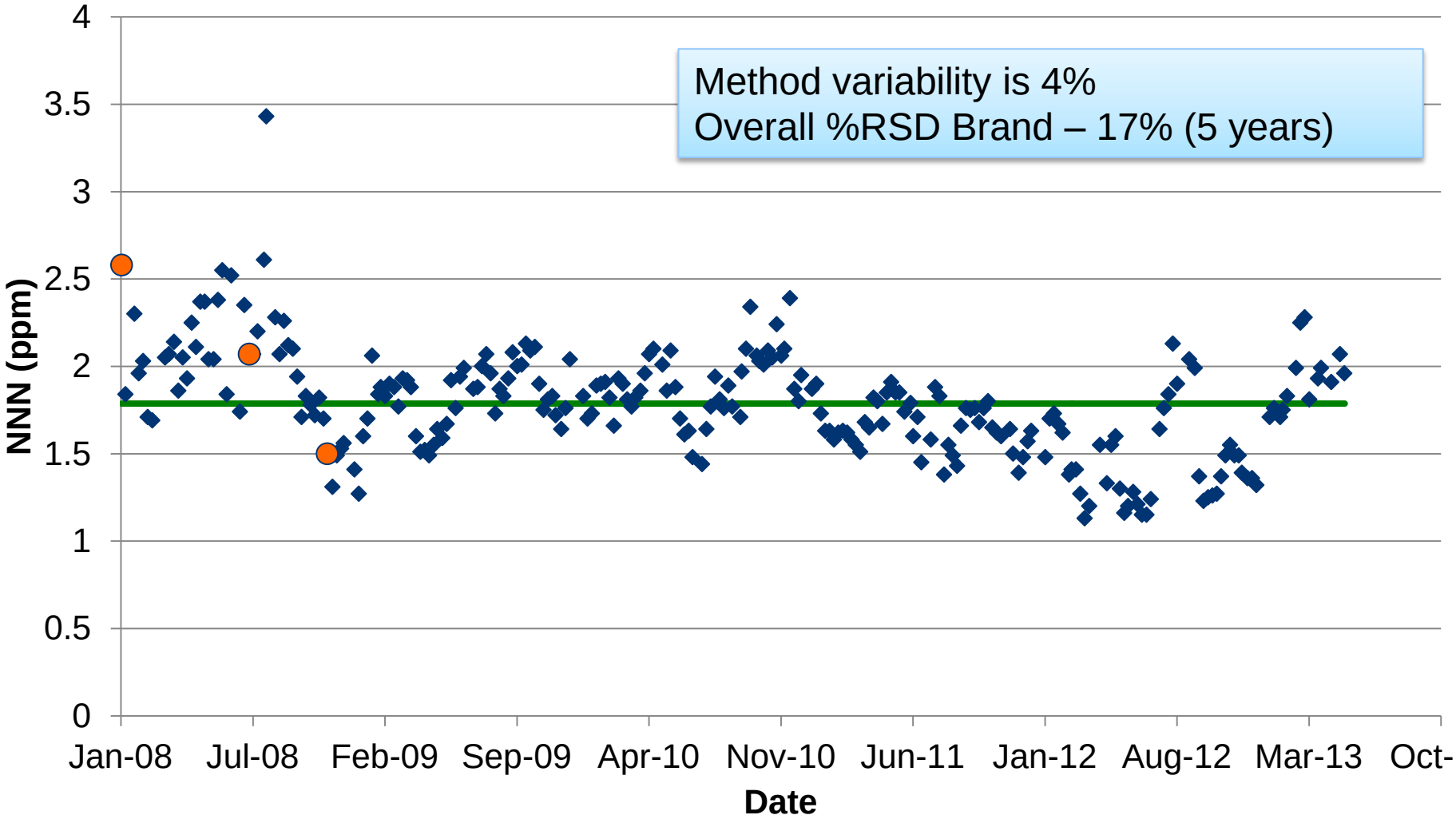
	Product A	Product B	Product C
Nicotine (mg/cig)	5%	9%	2%
CO (mg/cig)	7%	12%	14%
Ammonia (µg/cig)	9%	2%	5%
Carbonyls (µg/cig)	4% - 12%	6% - 16%	2% - 12%
VOCs (µg/cig)	9% - 17%	5% - 17%	2% - 14%
PAA (ng/cig)	10% - 24%	13% - 29%	7% - 20%
BaP (ng/cig)	4%	1%	20%
TSNA (ng/cig)	49% - 66%	21% - 22%	29% - 60%

Batch to Batch Filler Variability – Product A

	T1	T2	T3	Difference
Nicotine (mg/g)	19.0	20.0	17.5	13%
NNN (ng/g)	2611	1301	2068	67%
NNK (ng/g)	519	<LOQ	374	33%
As (ng/g)	256	270	237	13%
Cd (ng/g)	804	798	885	10%
Ammonia (µg/g)	1775	1902	1963	10%

3R4F filler TSNA variability 2% - 4%

Leaf TSNA Results over Time – Commercial Cigarettes



Sampled weekly, n=253

Difference Comparisons – ISO Smoking

	Intra-lab 3R4F	Temporal 3R4F	Batch to Batch Products*	Interlab[3-5]
Nicotine (mg/cig)	5%	7%	4% - 10%	16%
CO (mg/cig)	6%	7%	8% - 23%	17%
Ammonia (µg/cig)	10%	12%	17% - 23%	118%
Carbonyls (µg/cig)	7% - 12%	25% – 41%	9% - 31%	51% - 171%
VOCs (µg/cig)	7% - 10%	7% – 13%	2% - 28%	48% - 175%
PAA (ng/cig)	7% - 11%	5% – 21%	2% - 32%	88% - 100%
BaP (ng/cig)	8%	21%	8% - 20%	46%
TSNA (ng/cig)	7% - 9%	3% – 7%	30% - 58%	37%

Intra-lab 3R4F variability is based on long-term testing
Difference Calculations are shown as %Difference in reported means
*Range shown incorporates range among analytes and across Products A, B, and C

Key Findings

- Long-term intra-lab variability is approximately 10% based on 3R4F testing
- Short-term temporal variability was generally lower for reference products than commercial products
- Commercial product short term batch to batch variability was similar for ISO and CI
- Long-term variability was lower than short-term variability
- Intra-lab variability and batch to batch product variability were much less than inter-lab variability

Conclusions

- It is important to understand long-term variability of products
- Method tolerance ranges may need to be broader for testing beyond nicotine and CO
- Equivalence testing, rather than difference testing, may be worth consideration for statistical evaluations of product data
- Use of certified reference products, proficiency testing, and method standardization will lead to improved inter-lab variability

References

1. FDA meeting, Feb 14, 2013 (ISO, CI Smoking 3R4F, data not shown but are consistent with displayed information for references 3-5)

2. http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297828.pdf

3. CORESTA Collaborative Study Beiträge zur Tabakforschung International/Contributions to Tobacco Research Volume 23 - No. 4 - May 2009
(2R4F ISO Smoking)

4. CORESTA Collaborative Study *Beiträge zur Tabakforschung International/Contributions to Tobacco Research* Volume 25 - No. 4 - December 2012 (3R4F ISO Smoking)

5. CORESTA Collaborative Study 2011 CORESTA Monitor #6 #7 TNCO Coresta Website - February 2012 (CM6 ISO Smoking)