A Proposed Approach for Modeling HPHC Yields

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ABSTRACT

To ensure quality, consistency and supply security of its product portfolio over time, a company may need to make changes that affect all or much of its portfolio of products. In our proposed approach, instead of testing each product individually, we propose conducting a designed experiment of a subset of products that encompasses the major design characteristics of the manufacturer's portfolio and use statistical modeling to determine the harmful and potentially harmful constituent (HPHC) yield for the rest of the portfolio. Additionally, such a modeling approach could also potentially be used to generate supporting information for premarket submissions such as Substantial Equivalence Reports. To demonstrate feasibility, we used 30 representative products that cover the range of cigarette design and filler parameters of Philip Morris USA's (PM USA) entire portfolio. One set of 30 products was manufactured using current cigarette paper and another set using two different papers. The experiment was controlled to minimize product, manufacturing and analytical testing variations between the products with the two cigarette papers. Models were developed to correlate the HPHC yields of the changed product to yields of the control product. For model validation, 12 different products were randomly selected from the remaining products. The predicted yields from the model were compared with the measured yields. Model predictions were robust and differences between measured and predicted values were within the ISO repeatability limits, thereby demonstrating feasibility of our proposed approach.

INTRODUCTION

To ensure quality, consistency and supply security of its portfolio, a company may need to make changes (e.g. changing a processing step or using a raw material from an alternate supplier) that affect much of its portfolio of products.

Hypothesis: Depending on the nature of the change, HPHC yields of the changed product will be either equivalent, or can be predicted from those of the current product.

Proposed Approach

Use combination of designed experiments and statistical modeling to predict HPHC yields of changed products

Select a representative set of impacted products

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1. Manufacture two sets of selected products: Current and Proposed Change
2. Concurrently measure HPHCs for both sets of products

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Build models to correlate HPHC yields of Current & Changed products

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Use modeled data to report HPHC yields for the rest of changed products

OBJECTIVE

Demonstrate the feasibility of the proposed approach using a change in cigarette paper, as an example.

- Predict HPHC yields of the changed products (cigarettes made with two different papers) from HPHC yields of current market product

SAMPLE SELECTION & TESTING

Test Samples

- Sample selection was based on the following variables which may influence HPHC yields:
  - Cut filler type (Categorical)
  - Band width (Categorical*)
  - Permeability (Categorical*)
  - Ventilation
  - Filler weight
  - Plug RTD
  - Filter plug length
  - Circumference
  - Tobacco rod length
- At least one product from each of 25 possible categorical combinations was selected
- Multiple products within a categorical combination were selected based on the distribution of the remaining continuous variables and manufacturing volume representation
- 30 samples were selected to represent PM USA's entire portfolio comprising 147 products

**Values are treated as categorical*

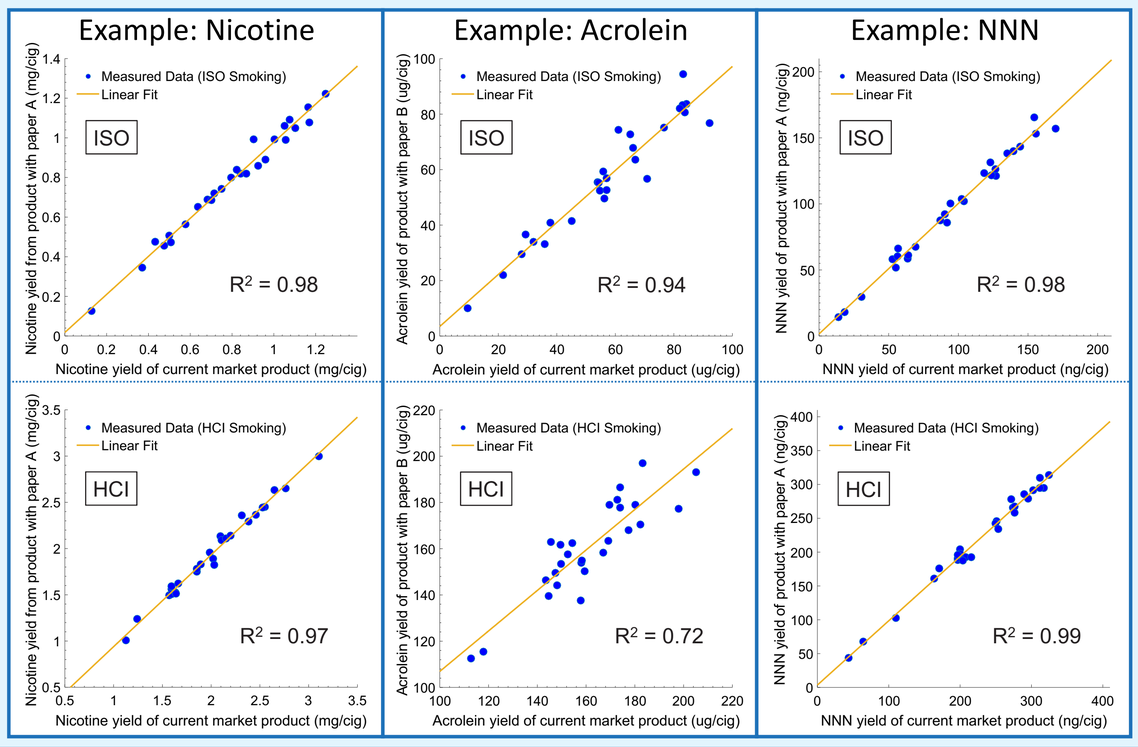
Validation Samples

- The validation sample set was selected to be 40% of the test set
- 12 samples were randomly selected from all remaining products not included in the test sample set

Method

- Smoking Conditions
  - Two testing regimes: ISO and Health Canada Intense (HCI)
- Products
  - Changed papers (A & B)
  - Current market
- Sampling Protocol
  - Cigarettes with current and two different papers were tested at the same time and under identical conditions
  - Three replicates were used for ISO and HCI testing

MODEL DEVELOPMENT

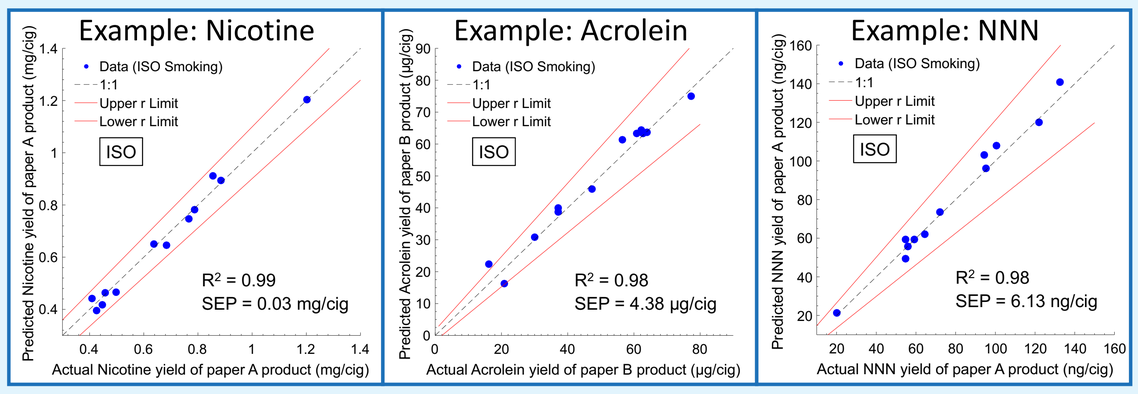


HPHC	Correlation Coefficient, R^2			
	ISO		Intense	
	Paper A	Paper B	Paper A	Paper B
1-Naphthylamine (ng/cig)	0.96	0.95	0.96	0.97
2-Naphthylamine (ng/cig)	0.96	0.93	0.97	0.97
4-Aminobiphenyl (ng/cig)	0.97	0.94	0.93	0.97
Acetaldehyde (µg/cig)	0.92	0.96	0.80	0.83
Acrolein (µg/cig)	0.91	0.94	0.73	0.72
Crotonaldehyde (µg/cig)	0.94	0.97	0.74	0.79
Formaldehyde (µg/cig)	0.93	0.96	0.90	0.96
B[a]P (ng/cig)	0.95	0.97	0.87	0.89
Carbon Monoxide (mg/cig)	0.92	0.95	0.93	0.92
Nicotine (mg/cig)	0.98	0.98	0.97	0.98
Tar (mg/cig)	0.98	0.98	0.96	0.97
NNN (ng/cig)	0.98	0.99	0.99	0.97
NNK (ng/cig)	0.98	0.99	0.94	0.96

- As expected, there is good correlation between HPHC yields of the current market product and products made with the two different papers (A & B)
- In some cases, lower model correlation coefficients may be due to high method variability for the measured constituent

Model Validation Results

- Models are validated by comparing measured HPHC yields of the validation samples to their predicted yields
- Models are considered acceptable if the predicted values do not differ significantly from method variability
- Model limits are based on repeatability from CORESTA studies[1-5]
  - In some cases, repeatability is adjusted based on differences in the number of replicates used in this study



HPHC	ISO Smoking							HCI Smoking						
	Method	Paper A			Paper B			Method	Paper A			Paper A		
	SE (r)	R^2	SEP	p-value	R^2	SEP	p-value	SE (r)	R^2	SEP	p-value	R^2	SEP	p-value
1-Naphthylamine (ng/cig)*	0.47	0.95	1.33	0.28	0.98	0.82	0.36	0.47	0.99	1.01	0.68	0.97	1.48	0.76
2-Naphthylamine (ng/cig)*	0.31	0.96	0.40	0.52	0.96	0.36	0.61	0.31	0.98	0.68	0.69	0.97	0.87	0.74
4-Aminobiphenyl (ng/cig)*	0.11	0.87	0.15	0.48	0.93	0.08	1.00	0.11	0.99	0.15	0.58	0.96	0.09	0.45
Acetaldehyde (µg/cig)	45.0	0.99	46.27	0.52	0.98	33.00	0.32	190.8	0.79	82.92	0.10	0.87	75.98	0.08
Acrolein (µg/cig)	3.9	0.96	4.06	0.52	0.98	4.38	0.57	9.4	0.79	13.52	0.71	0.89	10.67	0.58
Crotonaldehyde (µg/cig)	2.03	0.98	1.73	0.40	0.98	1.69	0.39	9.8	0.74	4.02	0.09	0.86	3.47	0.06
Formaldehyde (µg/cig)	4.67	0.98	4.26	0.44	0.97	4.10	0.42	20.4	0.97	5.34	0.02	0.98	6.20	0.04
B[a]P (ng/cig)	0.53	0.98	0.58	1.00	0.98	0.58	1.00	2.64	0.96	1.03	0.13	0.97	0.93	0.08
Carbon Monoxide (mg/cig)	0.64	0.96	0.91	0.09	0.98	0.94	0.07	1.17	0.77	3.09	0.27	0.83	2.18	0.35
Nicotine (mg/cig)	0.04	0.99	0.03	1.00	0.99	0.02	1.00	0.12	0.99	0.06	1.00	0.96	0.09	1.00
Tar (mg/cig)*	0.48	0.99	0.43	1.00	0.99	0.29	1.00	0.48	0.98	1.22	0.14	0.95	1.12	0.15
NNN (ng/cig)	15.76	0.98	6.13	0.08	0.99	3.51	0.01	45.86	0.99	8.49	0.01	0.98	10.76	0.02
NNK (ng/cig)	11.31	0.99	5.46	0.13	0.99	3.79	0.05	28.36	0.97	7.80	0.03	0.97	9.70	0.05

*ISO values used for HCI Smoking

p-values ≤ than 0.05: Statistically Significant difference between Standard Error of the Method Repeatability (SE(r)) and Standard Error of Model prediction (SEP)

R^2: Correlation between measured and predicted response

- In most cases, the predicted variability does not differ from the method repeatability
- For some constituents, the predicted variability is significantly lower than the method variability

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SUMMARY

- We proposed testing a subset of products and applying statistical modeling approach to predict the HPHC yields of a changed product from those of current products
- The approach was tested using change in cigarette papers as an example, and HPHC yields predicted by the model were found to be within the measurement variability of the smoke constituent
- We are working to expand the applicability of the approach to future proposed changes in process or material
- We will continue to communicate progress to the scientific and regulatory communities