Preclinical Testing of Flavors in E-vapor Products Part 4:

Flavor Transfer from the Liquid to the Aerosol for Inhalation Exposure

Jingjie Zhang

Tobacco Science Research Conference
September 17, 2019

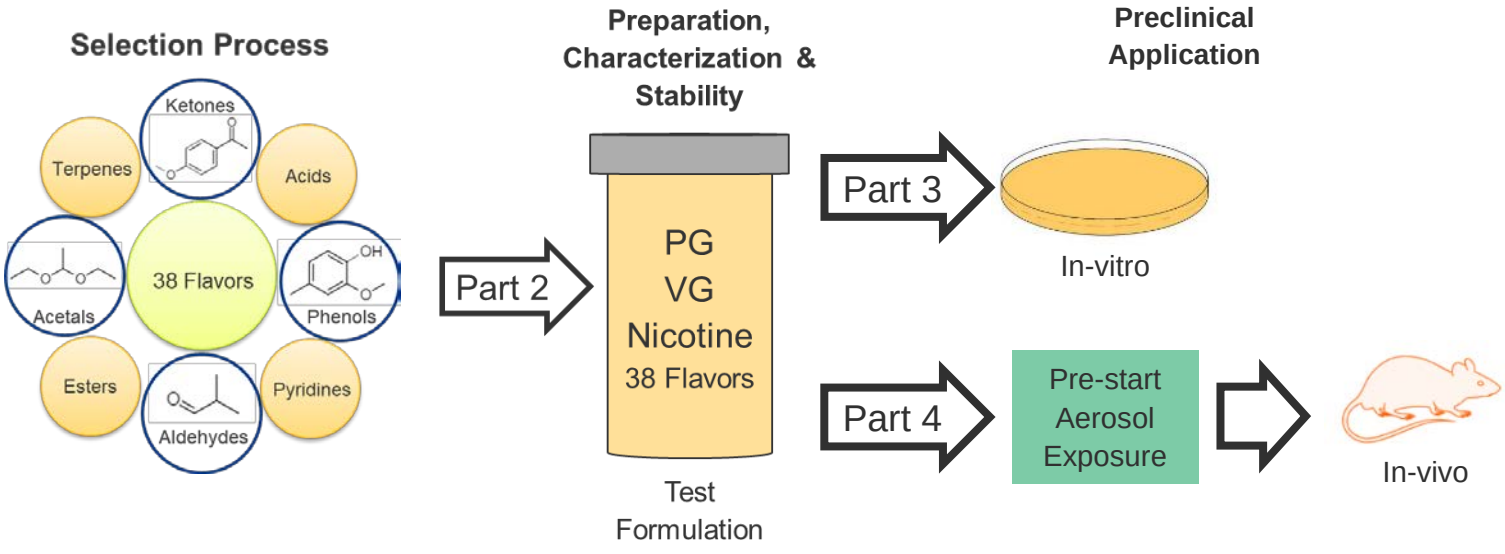
Altria
Altria Client Services

Overview

- Preclinical testing of flavors in e-vapor products, Part 1: selection of representative flavor mixtures for toxicological evaluations using a structural grouping approach
- Preclinical testing of flavors in e-vapor products, Part 2: preparation and stability characterization of representative flavor mixtures
- Preclinical testing of flavors in e-vapor products, Part 3: in vitro cytotoxicity and genotoxicity of representative flavor mixtures
- Preclinical testing of flavors in e-vapor products, Part 4: flavor transfer from the liquid to the aerosol for inhalation exposure

Altria
Altria Client Services

Overview



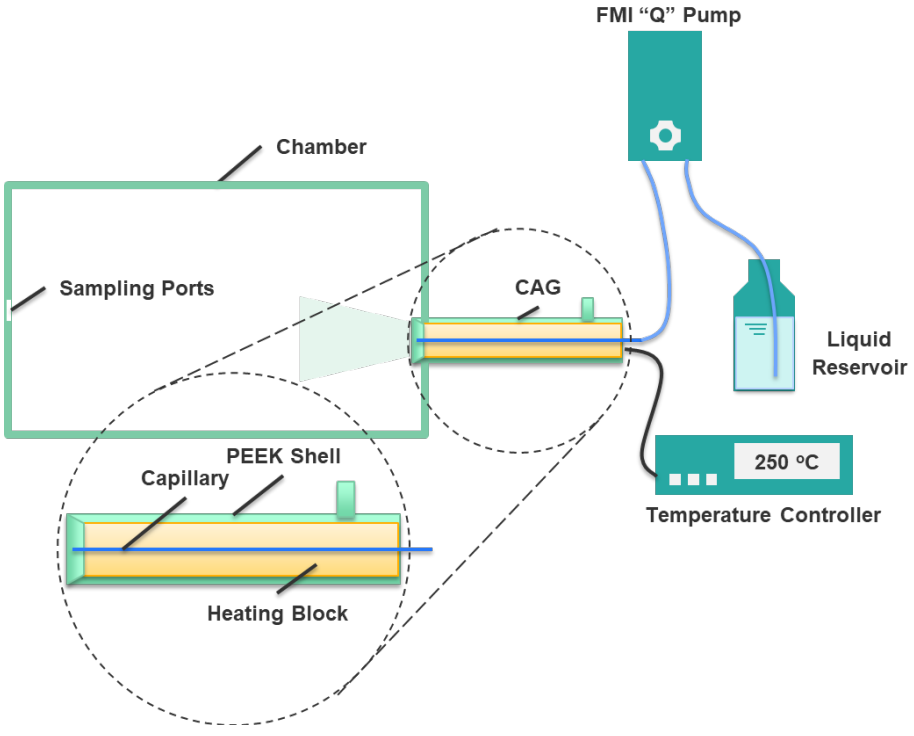
PG: propylene glycol
VG: vegetable glycerol

Objective

- To generate aerosols using designated test formulations
- To characterize the generated aerosols
- To confirm the flavor transfer from formulation to aerosols

Aerosol Generation

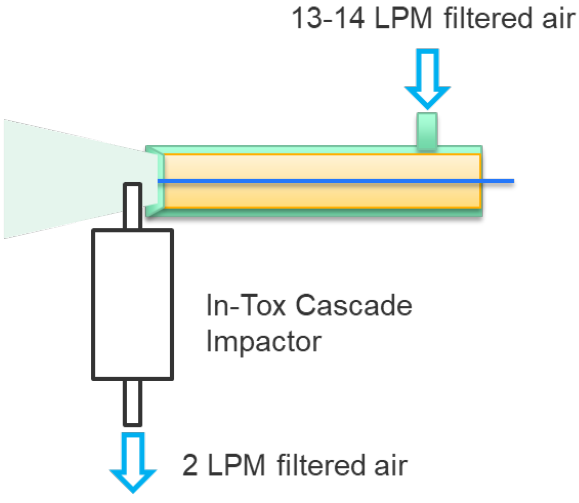
- Test Formulation with and without nicotine



CAG: Capillary Aerosol Generator

Aerosol Size Distribution

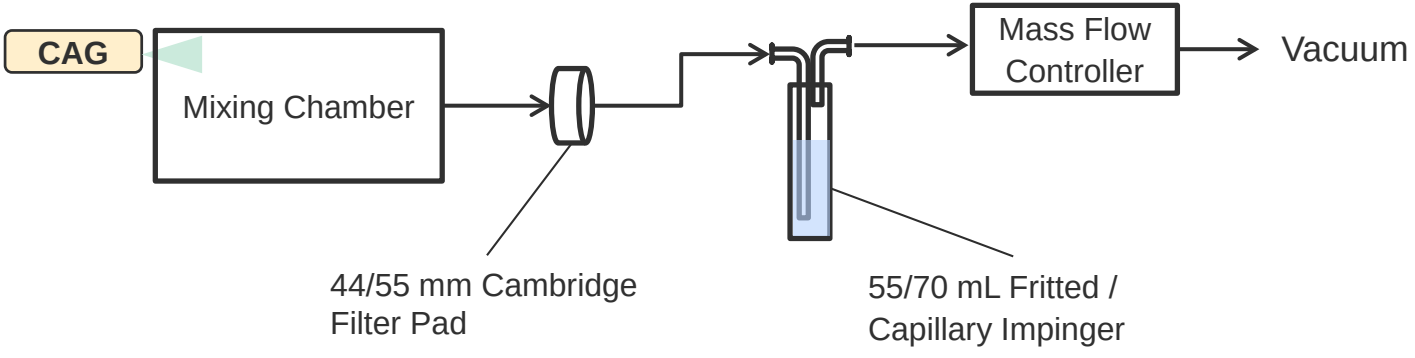
- Method
  - Cascade impactor



	Test Formulation w/ Nicotine (n = 4)	Test Formulation w/o Nicotine (n = 4)
MMAD (µm)	0.97 ± 0.07	1.23 ± 0.06
GSD	1.77 ± 0.18	1.82 ± 0.13

Aerosol Sampling for Chemical Analysis

Analyte of Interest	Cambridge Filter Pad	Impinger
Aerosol Mass	44 mm	No
Nicotine, PG, Glycerin	44 mm	No
Selected Carbonyls	44 mm	DNPH derivatization solution
Selected Flavors	55 mm	Ethanol (-70°C)
pH	No	Fritted; KCl solution



Analytical Characterization

	Test Formulation w/ Nicotine (N = 3)			Test Formulation w/o Nicotine (N = 3)		
Analyte	**Liquid**	**Aerosol**	**Transfer[b]**	**Liquid**	**Aerosol**	**Transfer[b]**
Aerosol Mass (mg)	NA	98.1±2.0	NA	NA	108.2±1.8	NA
Ethanol (mg/g)	20.44±0.13	BLOQ	NA	20.19±0.23	BLOQ	NA
Glycerol (mg/g)	144.3±0.3	146.2±2.1[a]	101%	146.1±0.5	147.1±3.1	101%
Nicotine (mg/g)	20.21±0.17	20.61±0.25[a]	102%	ND	ND	NA
PG (mg/g)	580.6±2.14	611.2±14.2[a]	105%	625.3±0.99	656.3±26.5	105%
Water (mg/g)	63.11±0.89	79.90±2.37[a]	127%[c]	55.81±0.71	73.81±0.71	132%[c]

a. The values were normalized by the collected aerosol mass.

b. The transfer was calculated as Transfer (%) = $\frac{Concentration\ in\ Aerosol\ (\frac{mg}{g})}{Concentration\ in\ E-liquid\ (\frac{mg}{g})} X\ 100\%$.

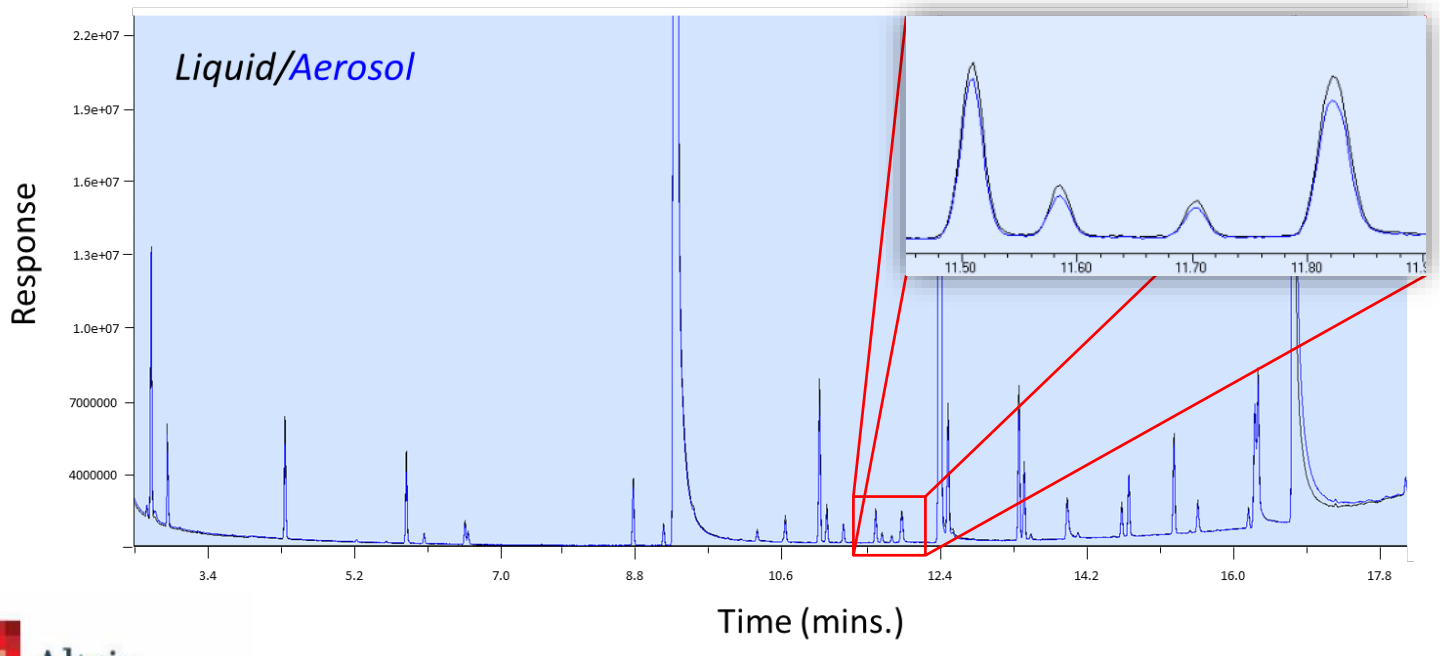
c. Water exceeded 100% by a wide margin due to the hygroscopicity of PG and Glycerin.

NA = not applied; ND = not detected; BLOQ = below the limit of quantification.

Altria
Altria Client Services

Flavor Transfer

- Test formulations contained 38 flavors.
- 22 out of 38 (Lab 1) were analyzed in both the liquid and the aerosol.



Selected Carbonyls in the Aerosol

	Blank (n = 3)	Carrier (PG/VG/Nicotine/ Water) (n = 3)	High w/ Nicotine (n = 3)	High w/o Nicotine (n = 3)
Aerosol Mass (mg)	100 mg	107.2 ± 5.4	106.7 ± 1.3	116.1 ± 1.5
Formaldehyde (µg/g) [c]	< LOQ	8.71 ± 0.57	4.98 ± 0.15	5.88 ± 0.24
Acetaldehyde (µg/g) [c]	3.09 ± 0.11	8.34 ± 0.89	Above 1000[b]	Above 1000[b]
Acrolein (µg/g) [c]	< LOD	1.63 ± 0.20	5.36 ± 0.65	2.37 ± 0.13
Crotonaldehyde (µg/g) [c]	< LOD	< LOD	10.57 ± 0.75	8.18 ± 0.17

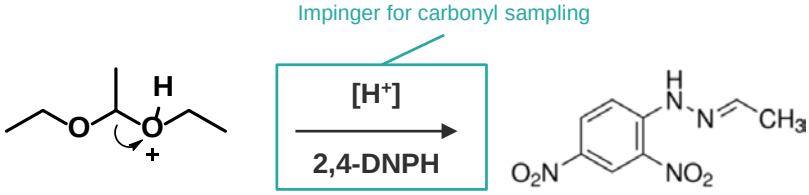
a. Assumes 100 mg for calculation purposes;
b. Approximations - Above Calibration Curve;
c. Reported values were normalized to the collected aerosol mass.

Where did acetaldehyde come from?

Altria
Altria Client Services

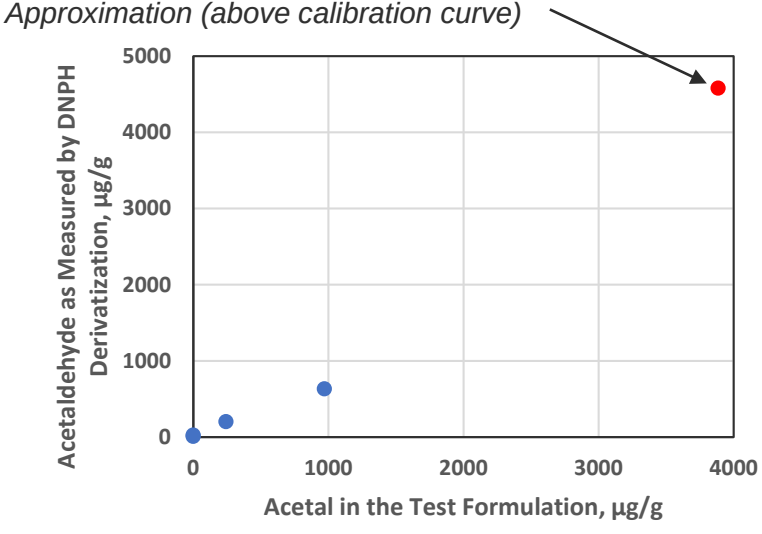
1,1-Diethoxyethane in Pre-blend Ic Detected as Acetaldehyde

- 1,1-diethoxyethane detected as acetaldehyde in the carbonyl analysis due to the sampling limitation
- 1,1-diethoxyethane as a flavor was transferred to the aerosol around 100% by GC-MS method (Lab 2).



1,1-Diethoxyethane (Acetal; CAS: 105-57-7)

Acetaldehyde - 2, 4-DNPH



1,1-Diethoxyethane (acetaldehyde diethyl **acetal**)

pH of the Aerosol

	Test Formulation w/o Nic	Test Formulation w/ Nic
Liquid pH (n = 3)	4.6	7.7
Aerosol pH (n = 3)	4.7	7.6

pH adjustment in the formulation?

	Test Formulation w/o Nic (pH adj. w/ NaOH)
Liquid pH (n = 1)	7.1
Aerosol pH (n=3)	4.6

After <1 hr

Always characterize the test atmosphere for confirmation.

Summary

- ✓ Flavor transfer from liquid formulation into the aerosol was confirmed.
- ✓ Particle size for both formulations (high with and without nicotine) tested were in the desired range (MMAD<1.6 µm, GSD<2).
- ✓ Nicotine, PG and glycerol matched in formulations and CAG aerosol for the test formulations.
- ✓ Selected carbonyls measured in CAG generated aerosols were consistent with previous studies.
- ✓ Aerosol generated from final formulations had a measured pH between 4 and 8.

Acknowledgements

Altria Client Services, Richmond, Virginia, USA

Cameron Smith
Chase Anderson
Nicholas McCutcheon
John Miller
K. Monica Lee