ONE MORE TIME: UNPROTONATED NICOTINE IN E-CIGARETTE AEROSOLS: IS IT REALLY THERE?

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Outline for presentation

- Nicotine in mainstream cigarette smoke (MSS) versus nicotine in e-cigarette aerosols
- pH values of e-liquids and e-cigarette aerosols
- Nonvolatile acids in e-liquids
- Experimental details and results
  - Aerosol pH determinations
  - Nicotine uptake by artificial saliva exposed to e-cig aerosols
- Unprotonated nicotine in e-cigarette aerosols
- Sensory
- Conclusions

Nicotine in MSS versus e-cigarette aerosols

- Key features of MSS
  - More than enough CO_2 and H_2O (GVP and PP) to give nascent H_2CO_3 to overcome basicity from NH_3 and nicotine
  - Numerous organic acids
  - Fats and waxes make smoke lipophilic
- Key features of e-cigarette aerosols (before "salts")
  - No CO_2 other than atmospheric (~ 400 ppm)
  - H_2O reported to be ~ 15% of TPM (aka ACM)
  - Little acidic material unless added to e-liquids as flavors
  - Nicotine in aerosol believed to be unprotonated based on pH determinations of aqueous solutions of e-liquids

pH values: e-liquids and e-cigarette aerosols

- pH values of concern by analogy to flawed reports of physiologically important levels of nicotine in MSS
- Pankow et al., *Chem. Res. Toxicol.*, 31, 431-434
  - Explanation of why published techniques for the determination of pH values of e-liquids gave inaccurate results
  - Reported ^{1}H NMR procedure to estimate unprotonated fraction of nicotine (α_{fb}) in e-liquids and aerosols
  - Requires expensive instrumentation, skilled technicians
  - Gave α_{fb} of~0.06 for JUUL e-liquids; others 0.68 to 0.84
  - Post vaporization α_{fb} similar to those of e-liquids
- Is something else going on?

Nonvolatile acids in e-liquids

- US 9,215,895, Nicotine salt formulations …
  - Bowen and Xing, 2015, assigned to PAX Labs, Inc.
  - Nicotine salt formulations where acid used has vapor pressure >200 mm Hg at 200° C
  - Acids used to form salts include benzoic, citric, levulinic, pyruvic, and salicylic (typically 2 to 4% in e-liquid)
  - Claims rapid rise in blood nicotine typical of conventional cigarette, and much faster than e-liquid without acid
- Benzoic acid known to be used commercially
  - Easy to use in making your own e-liquids
  - Malic, quinic, and vanillic also work 1:1 with nicotine

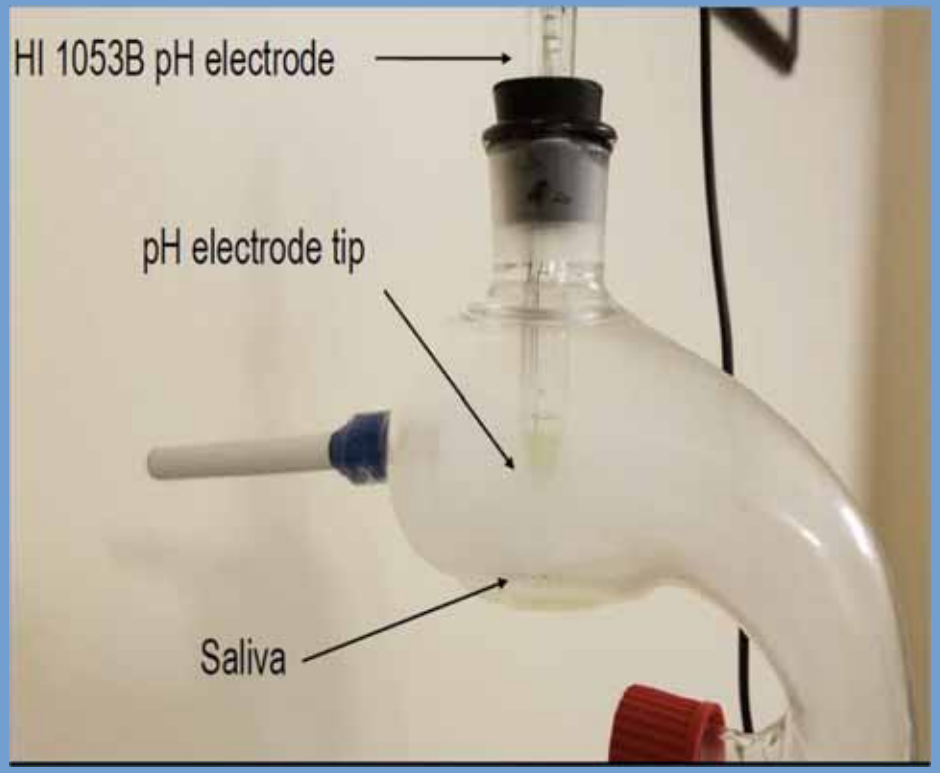
Experimental details – 1

- L&ALLC Model IIIb µ-processor-controlled, constant-vacuum, square-wave e-cigarette puffing system; puffing regimen of 55/3/30 (CORESTA Recommended Method No. 81)
- Flow control by Swagelok SS-4MG-SL 10-turn metering valve acting as critical flow orifice
- Flow checked with Sigma-Aldrich 20414 500-mL bubble meter with Cerulean SC#59138 Restrictor 10CSM (calibrated)(1 kPa)

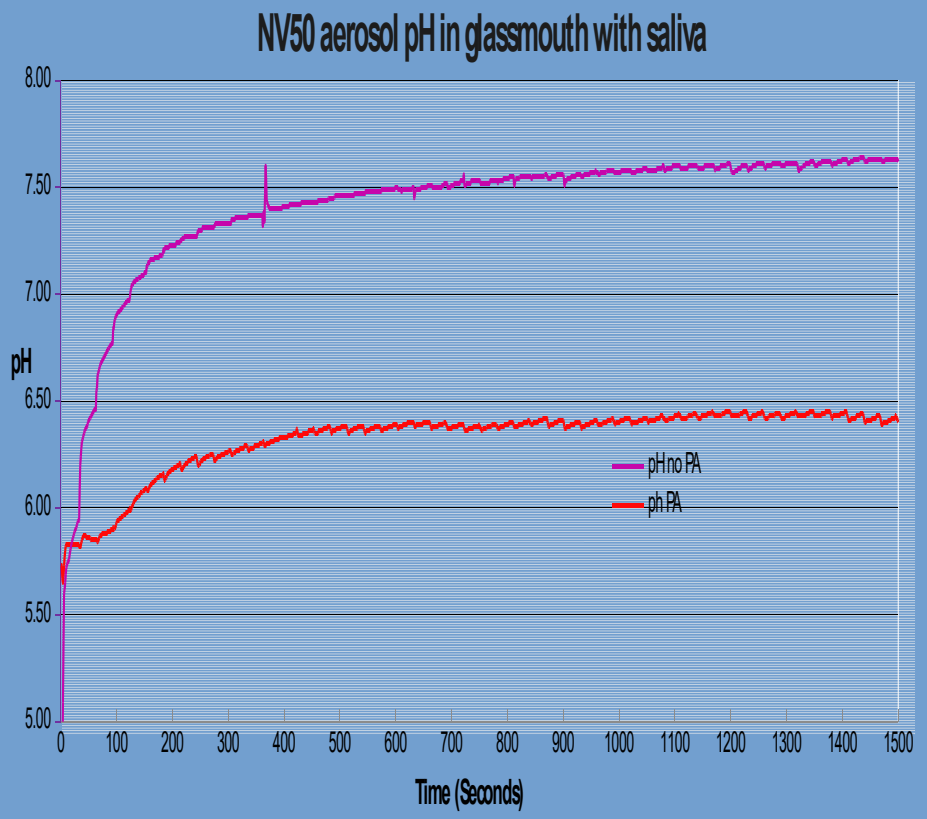
Experimental details – 2

- pH-Instrumentation – Hach H260G meter with Hanna Instruments HI 1053B (conical) pH electrode
- Hach Data Logger software (running under Windows 10 Pro) used to acquire and process pH data
- Saliva (Pickering 304) exposure done in glassmouth (Honeycutt, B&W, 1985, http://industrydocuments.library.ucsf.edu/tobacco/docs/jfbp0135) modified with depression (≈10 mL) for saliva and top port for pH probe, 50 puffs/run (25 puffs/run for initial assessments)

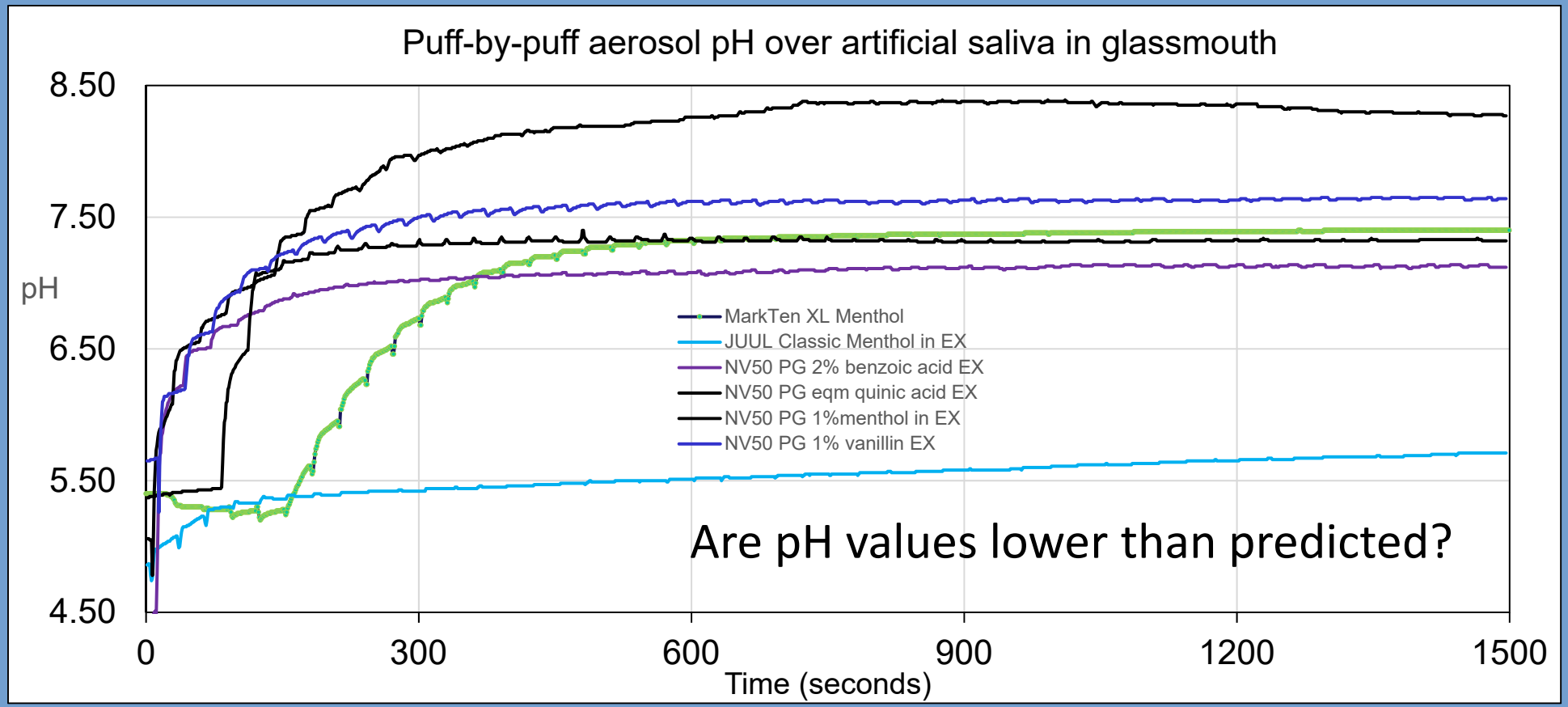
Experimental details – 3



Glassmouth trap with Conical tip electrode



Unexpected results 1: CO_2 effect?



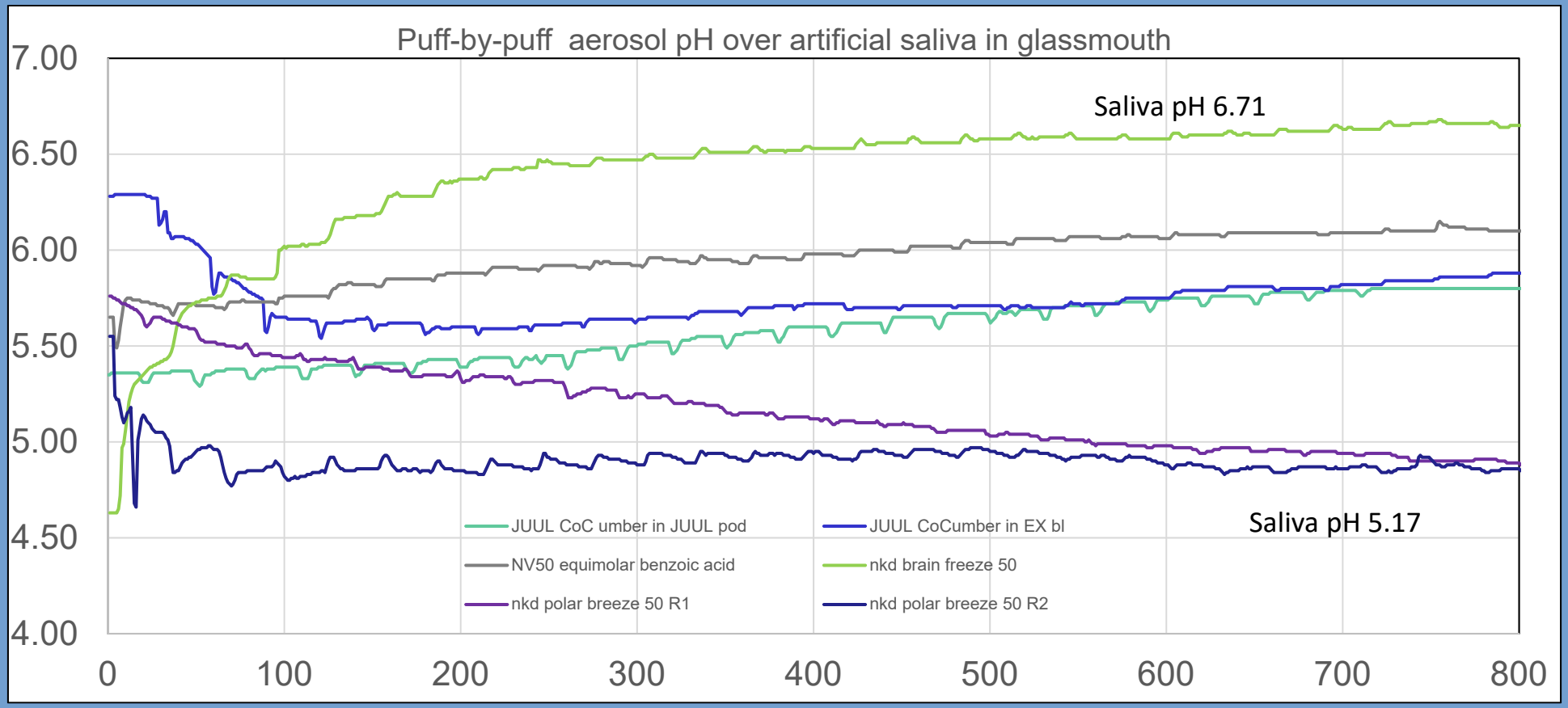
Unexpected results 2: saliva pH

Device or e-liquid in EX cartomizer	Aerosol pH	Saliva pH
MarkTen XL Menthol	7.40	7.11
JUUL Classic Menthol in EX	5.71	6.69
NV50 PG 2% benzoic acid EX	7.12	7.08
NV50 PG equimolar quinic acid EX	7.32	7.08
NV50 PG 1% menthol in EX	8.27	7.75
NV50 PG 1% vanillin EX	7.64	7.60

Hypotheses on what may be happening

- Atmospheric CO_2 may lower aerosol pH values
  - A study with e-liquids of known composition showed the ACM (~TPM) contained about 15% water
  - Supporting information for Pankow et al. shows how atmospheric water may affect pH results obtained after water dilution of e-liquids
- Solid acids (e.g., benzoic) apparently do not volatilize when e-liquids are vaped and result in decreased aerosol pH values as determined in glassmouth
- Aerosol pH values then similar to those of MSS

Some more puff-by-puff data



Unprotonated nicotine in e-cig aerosols

- Estimates of percent unprotonated nicotine in GVP can be made using the following equations
  - $K_{p,nicotine} = (f_{om}760RT)/(MW_{om}\gamma_{nicotine}p_{Lo,nicotine}10^6)$
  - $P_{g,nicotine}(\%) = 100\%\{1/(1 + K_{p,nicotine}TSP)\}$
- Estimates of MW_{om} can be made using data from CORESTA EVAP study of ACM weight, composition
  - $MW_{om} \approx 52$ g/mol, TSP $\approx 9.76 \times 10^7$ µg/m^3, $f_{om} \approx 1$
  - $K_{p,nicotine} \approx 1.67 \times 10^{-5}$, log $K_{p,nicotine} \approx -4.78$
- $\gamma_{nicotine}$ would need to be > 20 for $P_{g,nicotine}(\%) > 1\%$
  - Similar values have been reported for nicotine in water
  - Banyasz, The Physical Chemistry of Nicotine (1998)

Sensory

- Neither the NMR instrument nor the pH electrode in the glassmouth are representative of human vaping experiences
- However, analyses of aerosol constituents absorbed by the saliva should aid in understanding the sensory properties of the aerosols and the e-liquids from which they are generated
- Addition of benzoic acid reduces irritation, but can also give an off-taste

Conclusions

- Use of the glassmouth for the determination of aerosol pH appears to give the same information on nicotine protonation as given by more complicated and expensive techniques
- Estimations based on the weight and composition of the ACM during machine vaping of e-cigarettes can be used to estimate unprotonated nicotine in the gas-vapor phase (GVP) of e-cigarette aerosols