

# 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  $\text{CO}_2$  and  $\text{H}_2\text{O}$  (GVP and PP) to give nascent  $\text{H}_2\text{CO}_3$  to overcome basicity from  $\text{NH}_3$  and nicotine
  - Numerous organic acids
  - Fats and waxes make smoke lipophilic
- Key features of e-cigarette aerosols (before “salts”)
  - No  $\text{CO}_2$  other than atmospheric (~ 400 ppm)
  - $\text{H}_2\text{O}$  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  $^1\text{H}$  NMR procedure to estimate unprotonated fraction of nicotine ( $\alpha_{fb}$ ) in e-liquids and aerosols
  - Requires expensive instrumentation, skilled technicians
  - Gave  $\alpha_{fb}$  of ~0.06 for JUUL e-liquids; others 0.68 to 0.84
  - Post vaporization  $\alpha_{fb}$  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

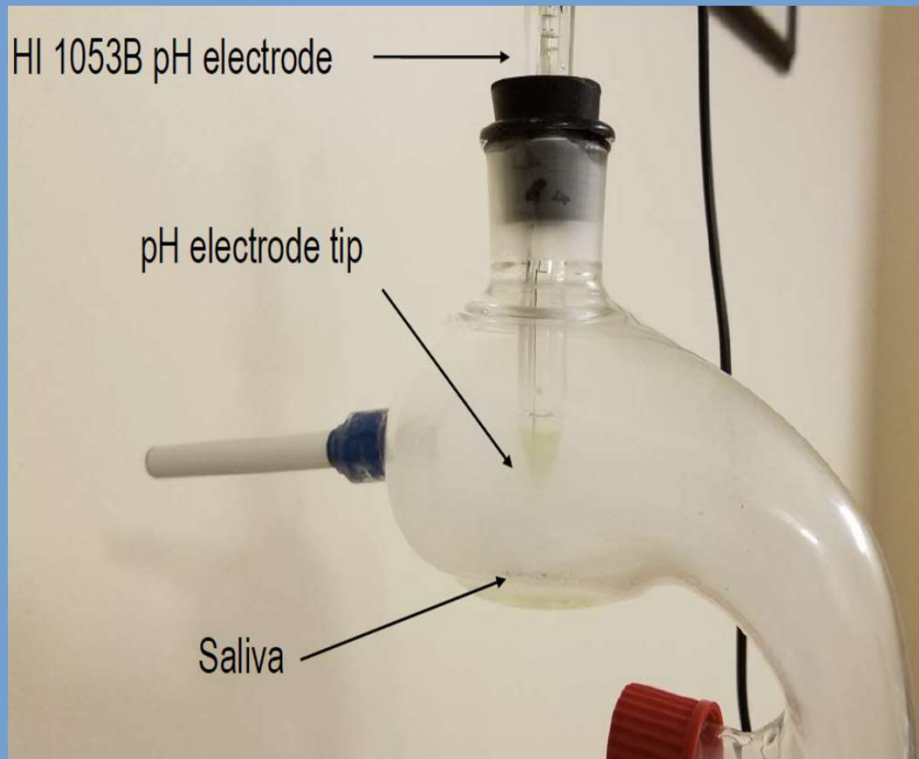
# Experimental details – 1

- L&ALLC Model IIIb  $\mu$ -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)

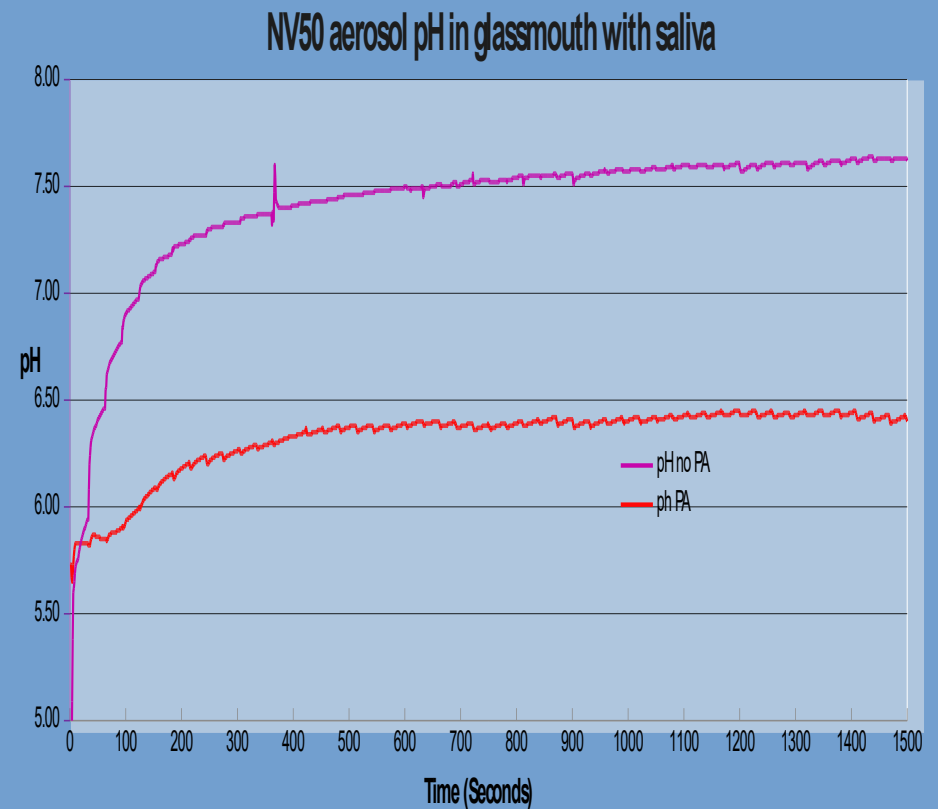
## Experimental details – 2

- 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 ( $\approx 10$  mL) for saliva and top port for pH probe, 50 puffs/run (25 puffs/run for initial assessments)

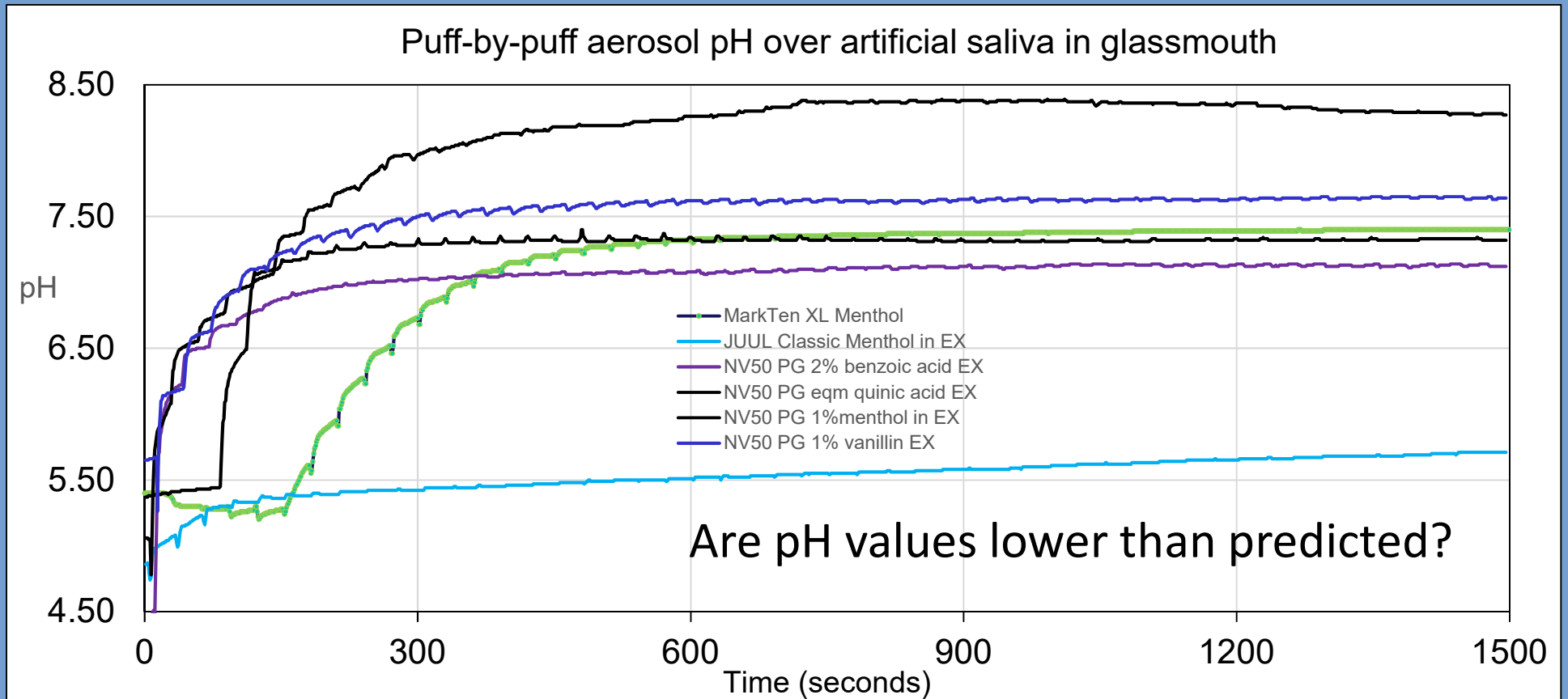
# Experimental details – 3



Glassmouth trap with Conical tip electrode



# Unexpected results 1: CO<sub>2</sub> effect?



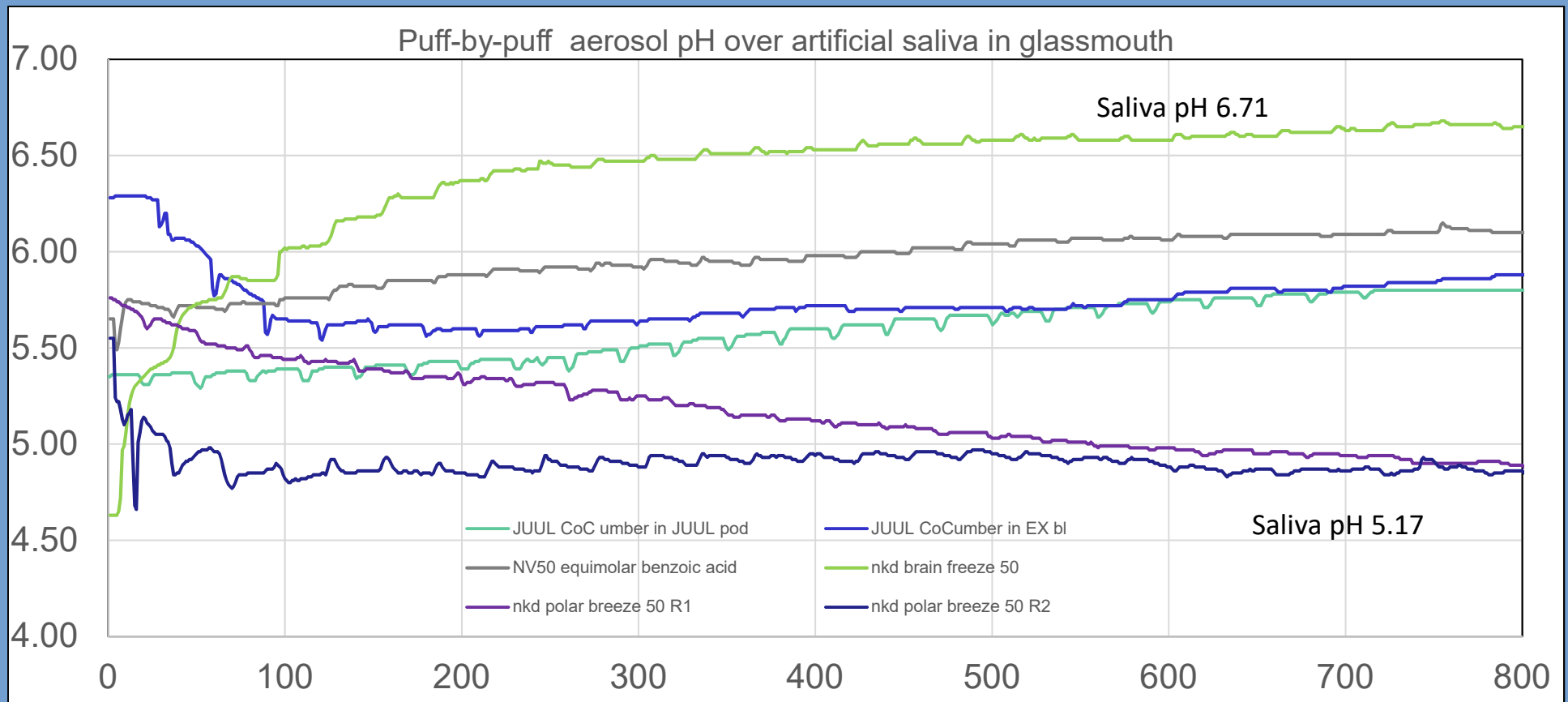
## Unexpected results 2: saliva pH

| 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<sub>2</sub> 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
  - $K_{p,\text{nicotine}} = (f_{\text{om}} 760 RT) / (MW_{\text{om}} \gamma_{\text{nicotine}} p_{\text{Lo,nicotine}} 10^6)$
  - $P_{g,\text{nicotine}}(\%) = 100\% \{1 / (1 + K_{p,\text{nicotine}} \text{TSP})\}$
- Estimates of  $MW_{\text{om}}$  can be made using data from CORESTA EVAP study of ACM weight, composition
  - $MW_{\text{om}} \approx 52 \text{ g/mol}$ ,  $\text{TSP} \approx 9.76 \times 10^7 \text{ } \mu\text{g/m}^3$ ,  $f_{\text{om}} \approx 1$
  - $K_{p,\text{nicotine}} \approx 1.67 \times 10^{-5}$ ,  $\log K_{p,\text{nicotine}} \approx -4.78$
- $\gamma_{\text{nicotine}}$  would need to be  $> 20$  for  $P_{g,\text{nicotine}}(\%) > 1\%$ 
  - 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