

Nicotine Uptake Following the Use of E-liquids with Different Organic Acid Salts and Nicotine Concentrations among Adult Smokers

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Introduction

- Nicotine concentration, device characteristics and user behavior influence nicotine pharmacokinetics from electronic nicotine delivery systems (ENDS)¹⁻³
- When nicotine is combined with an organic acid its freebase becomes protonated and forms a salt⁴
- Evidence suggests that ENDS using nicotine salt (vs. freebase) e-liquids more efficiently deliver nicotine^{5,6}
- However, there are numerous organic acids used in ENDS products (e.g., Citric, Benzoic), and the effects of individual acids on nicotine delivery is not widely characterized
- This controlled laboratory study assessed 11 different organic acids to evaluate the effects of nicotine-salt vs. freebase formulation as well as the effect of nicotine concentration on nicotine pharmacokinetics (PK).

Methods

- Design** - Parallel 22-arm controlled laboratory study
- Participants - N=184 adult smokers (N=31-37 per arm)
- Mean age = 37.2 years (SD=10.5), 63.3% male, 55.9% white
- On average, participants smoked 14.3 cigarettes/day (SD=6.5) and smoked for 20.2 years (11.2); 7.9% had ever-used ENDS
- Materials** - 21 non-commercialized test e-liquids (Table 1)
 - 20 nicotine-salt (11 total acids; 1.5% and 5.0% nicotine)
 - 1 freebase (1.5% nicotine)
- All e-liquids were tobacco-flavored and tested in a JUUL device
- Usual brand (UB) cigarette was used as a comparator
- Procedure** - nicotine PK was assessed following controlled use of test products (10 puffs) after five minutes
- Plasma nicotine concentrations were assessed 5 minutes prior-to (-5) and 1.5, 3, 5, 6, 7, 8, 10, 15, 30, 60, 90 and 120 minutes following the start of each product use
- PK endpoints were
 - baseline-adjusted peak nicotine concentration ($C_{\max\text{-BL}}$),

- baseline-adjusted total nicotine exposure after five minutes ($AUC_{0-5\text{-BL}}$), and
- time to peak nicotine concentration (T_{\max})
- Primary PK analysis – tests compared each nicotine salt e-liquid to the freebase control
 - $C_{\max\text{-BL}}$ and $AUC_{0-5\text{-BL}}$ were tested using two-sample t-tests
 - T_{\max} was tested using the Wilcoxon signed rank test

Conclusions

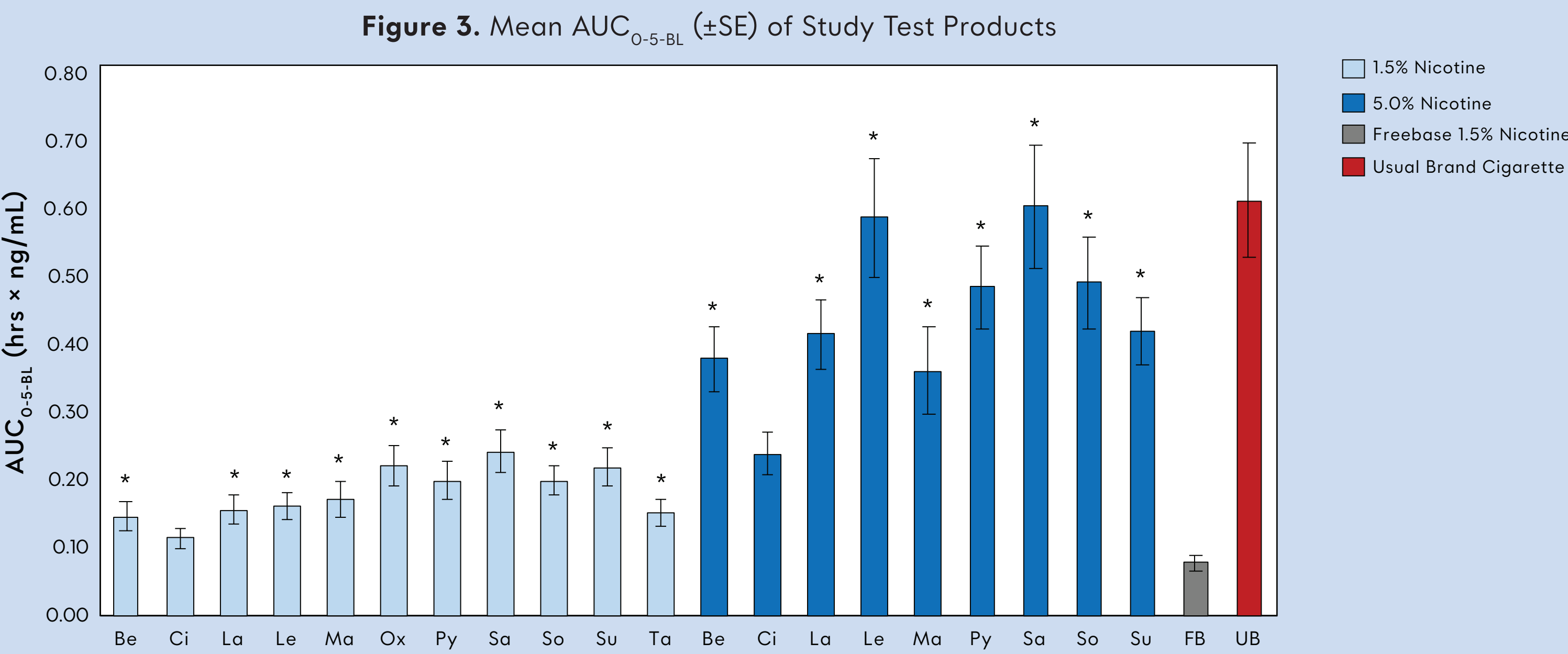
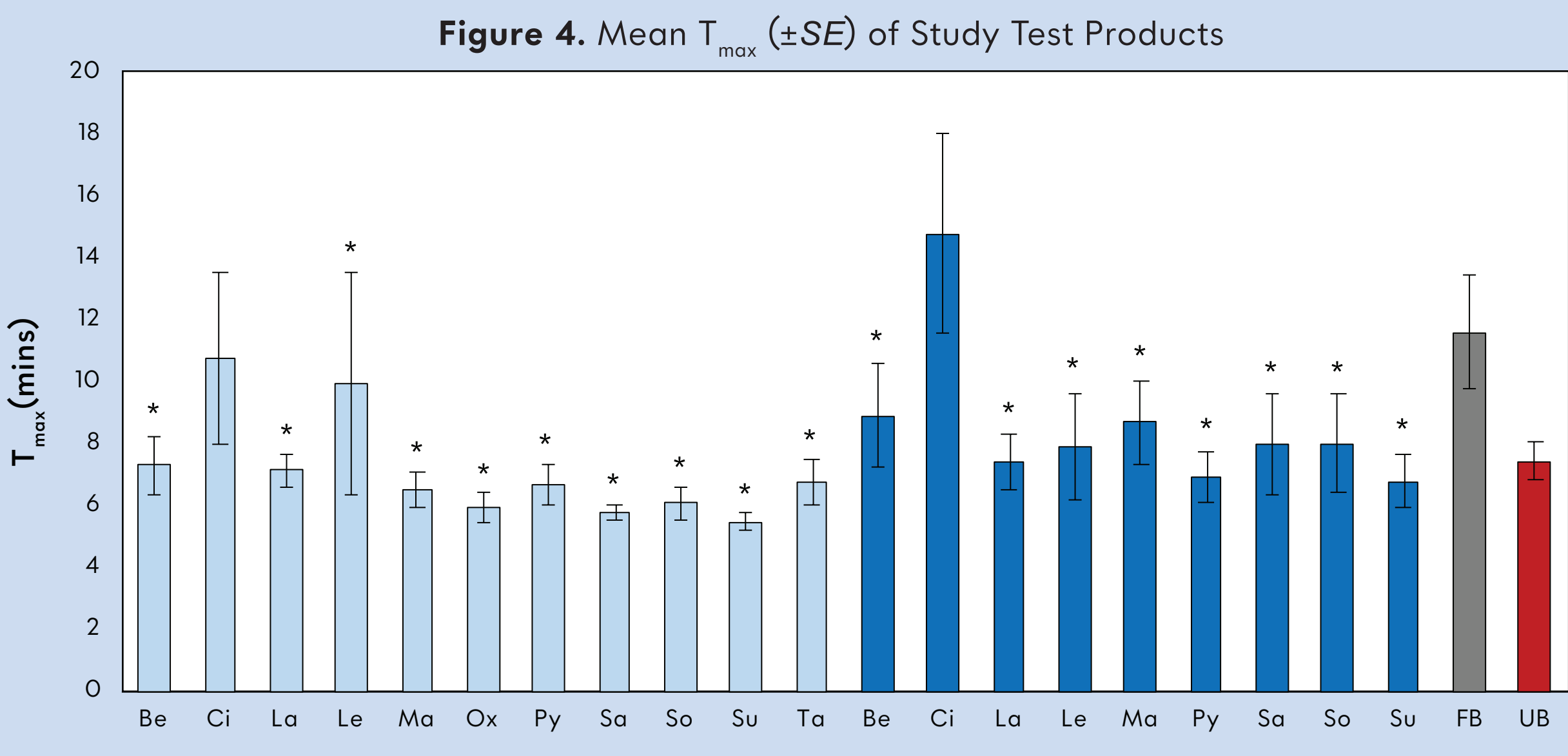
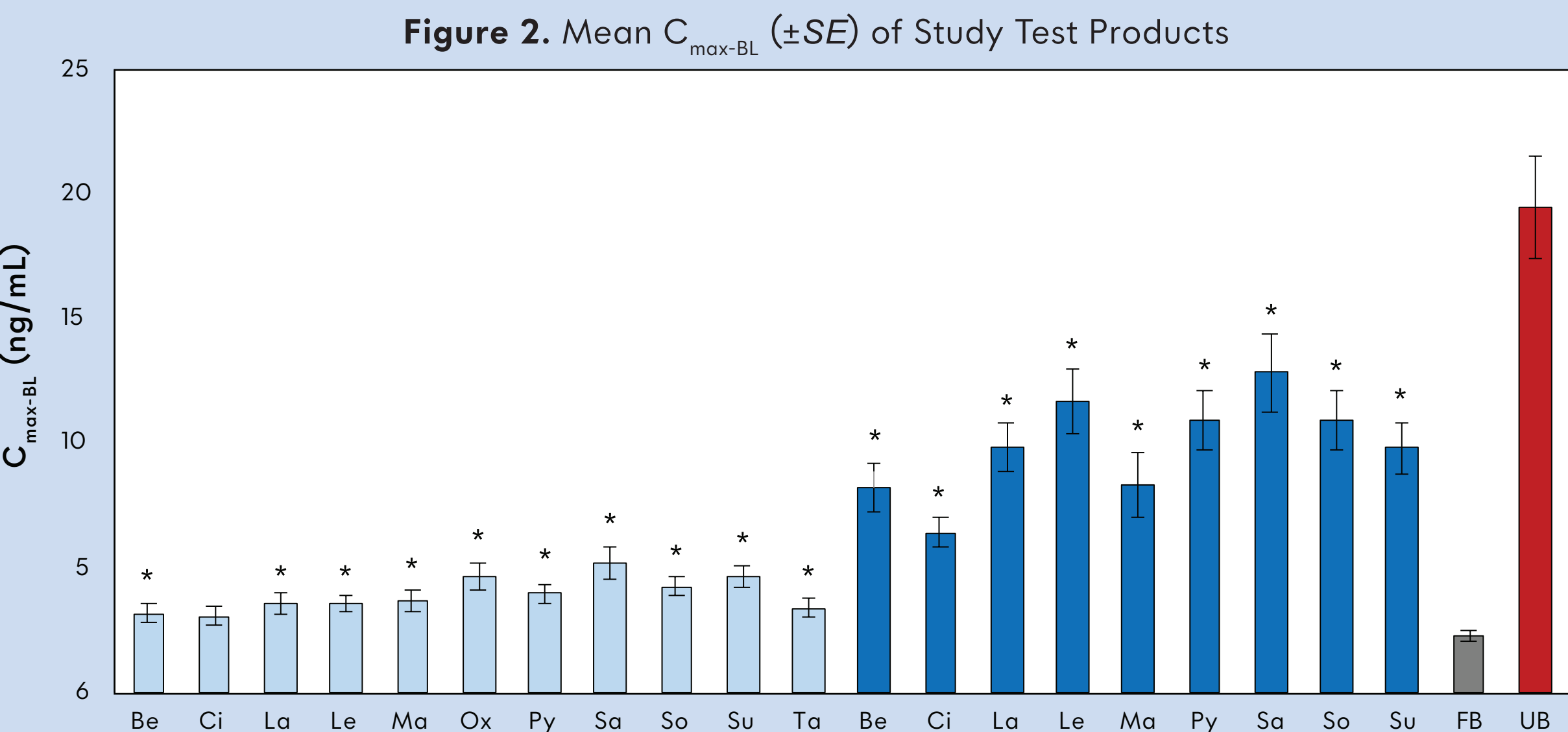
- All tested e-liquids delivered lower peak nicotine levels, and less nicotine in the first five minutes than cigarettes did but with comparable kinetics (except for Citric acid)
- When used in a JUUL device, e-liquids with higher nicotine concentrations (5.0% vs. 1.5%) delivered more nicotine
- Nicotine salt-based e-liquids (other than nicotine citrate) delivered statistically significantly more nicotine than did freebase e-liquids
- Nicotine exposure over the first 5 minutes from e-liquids with Benzoic acid (a variation of which is used in commercial JUULpods) was greater than Citric acid but lower than other acids (e.g., Salicylic)

Results

- When nicotine concentration was held constant (at 1.5%), all nicotine-salt e-liquids except Citric acid delivered significantly more nicotine than freebase (**Figures 2-3**)
- Among salt formulations, Benzoic acid was greater on $C_{\max\text{-BL}}$ and $AUC_{0-5\text{-BL}}$ than Citric acid
- Salicylic acid yielded the highest peak nicotine levels
- All nicotine-salt e-liquids, except Citric acid, had faster Tmax than freebase (**Figure 4**)
- All e-liquids tested had lower mean $C_{\max\text{-BL}}$ (19.5 ng/mL) and $AUC_{0-5\text{-BL}}$ (0.60 hrs×ng/mL) than UB cigarette (**Figures 2-3**)

Figure 1. Nicotine Formulation and Concentration of e-Liquids Tested in Study

Nicotine Concentration	Nicotine Formulation (Organic Acid or Freebase)											
	Benzoic (Be)	Malic (Ma)	Levulinic (Le)	Citric (Ci)	Lactic (La)	Pyruvic (Py)	Succinic (Su)	Salicylic (Sa)	Sorbic (So)	Oxalic (Ox)	Tartaric (Ta)	Freebase (FB)
1.5% (18 mg/mL)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5.0% (59 mg/mL)	✓	✓	✓	✓	✓	✓	✓	✓	✓	—	—	—



Note. Abbreviations: Be, benzoic acid; Ci, citric acid; FB, free-base; La, lactic acid; Le, levulinic acid; Ma, malic acid; Ox, oxalic acid; Py, pyruvic acid; Sa, salicylic acid; So, sorbic acid; Su, succinic acid; Ta, tartaric acid; UB, usual brand cigarette. *Significantly greater than freebase (p<0.05).

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