NICOTINE PHARMACOKINETICS ASSESSMENTS OF TWO TYPES OF E-CIGARETTES COMPARED TO CONVENTIONAL CIGARETTES: TWO RANDOMIZED, CROSSOVER STUDIES

D. YUKI[*], L. GILES, S. HARBO, A. HEMSLEY

JT International SA, Geneva, Switzerland

[*] Now at Japan Tobacco Inc., Tokyo, Japan

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Introduction

- The nicotine pharmacokinetics (PK) of new tobacco products have been getting attention from regulatory bodies as part of abuse liability assessments [1-4].

- The nicotine PK of various kinds of e-cigarettes have been assessed and reported to have lower or similar nicotine exposures compared to combustible cigarettes [5-8].

- It has been also reported that the nicotine PK of e-cigarettes is influenced by a combination of many factors, including e-liquid composition, user behavior and device characteristics [8].

- Two clinical studies were conducted to evaluate the nicotine PK parameters and assess nicotine consumption of two different types of e-cigarette with several flavor variants, under similar study protocols.

Study Products

Study	Code	Product	Device type	Flavor	Nicotine content of e-liquid (w/w%)
Study 1	A	eDNC1.0a	Cig-a-like	Tobacco	2.4 w/w%
	B	eDNC1.0a	Cig-a-like	Cherry	2.4 w/w%
	C	eDNC1.0a	Cig-a-like	Menthol	2.4 w/w%
	D	Conventional cigarettes	N/A	N/A	N/A
	E	Nicotine gum	N/A	N/A	N/A
	F	Reference e-cigarette	Cig-a-like	Tobacco	2.4 w/w%
Study 2	A	eDNC2.0a	Closed tank	Tobacco	1.8 w/w%
	B	eDNC2.0a	Closed tank	Menthol	1.8 w/w%
	C	eDNC2.0a	Closed tank	Cherry	1.5 w/w%
	D	eDNC2.0a	Closed tank	Berry Mint	1.5 w/w%
	E	Conventional cigarettes	N/A	N/A	N/A
	F	Nicotine inhaler	N/A	N/A	N/A
	G	Reference e-cigarette	Closed tank	Tobacco	3.0 w/w%

- **Cig-a-like e-cigarette, eDNC1.0a** (Logic Power) with three variants of flavored e-liquid

Rechargeable Battery Unit   Replaceable Cartridge

- **Closed tank e-cigarette, eDNC2.0a** (Logic PRO) with four variants of flavored e-liquid

Battery Unit   Pre-filled e-liquid capsule   Capsule Case

* Abbreviation: *eDNC1.0a = electronic direct heating nicotine system platform 1 generation 0 version a*
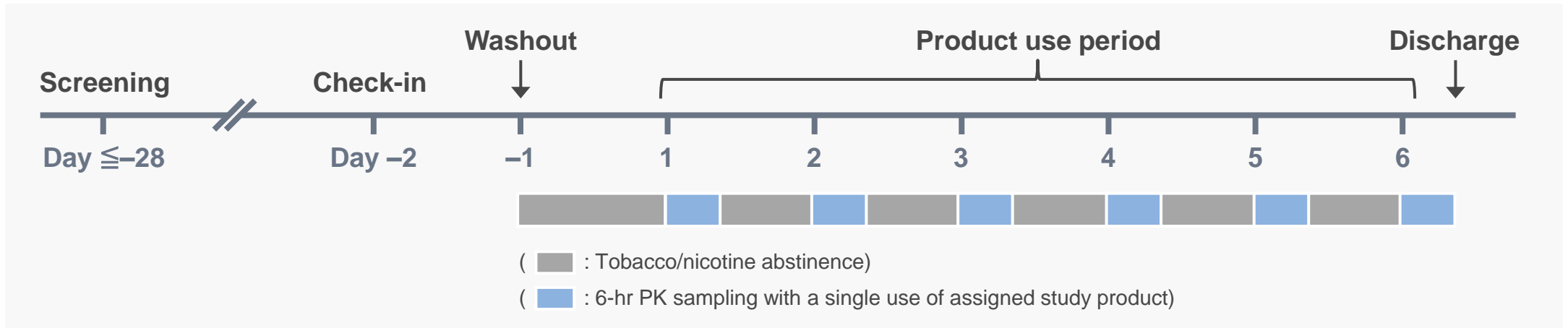   *eDNC2.0a = electronic direct heating nicotine system platform 2 generation 0 version a*

Study Designs

Designs

The two studies were randomized, open-label, controlled crossover studies*.

The objectives were to evaluate the nicotine PK parameters following a single *ad libitum* use of test e-cigarettes, as well as to assess subjective effects and nicotine consumption (only of e-cigarettes) in healthy US adults who smoke cigarette.

Study 1 (6-period crossover, 8-day confinement)

Washout

Product use period

Discharge

Screening

Check-in

Day ≦−28   Day −2   −1   1   2   3   4   5   6

(▮ : Tobacco/nicotine abstinence)

(▮ : 6-hr PK sampling with a single use of assigned study product)

Study 2 (7-period crossover, 9-day confinement)

(Same as above, although one day longer)

* The study was approved by the IRB responsible for review and approval and adhered to the ethical standards of the Declaration of Helsinki, applicable sections of the U.S. Code of Federal Regulations, and ICH E6 GCP. All participants gave written informed consent to participate in the study.

Study Designs

◆ **Product use regimen**

Study	Code	Product	Device type	Flavor	Nicotine content of e-liquid (w/w%)	Regimen
Study 1	A	eDNC1.0a	Cig-a-like	Tobacco	2.4 w/w%	*ad libitum*, 5 min use
	B	eDNC1.0a	Cig-a-like	Cherry	2.4 w/w%	*ad libitum*, 5 min use
	C	eDNC1.0a	Cig-a-like	Menthol	2.4 w/w%	*ad libitum*, 5 min use
	D	Conventional cigarettes	N/A	N/A	N/A	one cigarette
	E	Nicotine gum	N/A	N/A	N/A	30 min use
	F	Reference e-cigarette	Cig-a-like	Tobacco	2.4 w/w%	*ad libitum*, 5 min use
Study 2	A	eDNC2.0a	Closed tank	Tobacco	1.8 w/w%	*ad libitum*, 5 min use
	B	eDNC2.0a	Closed tank	Menthol	1.8 w/w%	*ad libitum*, 5 min use
	C	eDNC2.0a	Closed tank	Cherry	1.5 w/w%	*ad libitum*, 5 min use
	D	eDNC2.0a	Closed tank	Berry Mint	1.5 w/w%	*ad libitum*, 5 min use
	E	Conventional cigarettes	N/A	N/A	N/A	one cigarette
	F	Nicotine inhaler	N/A	N/A	N/A	20 min use
	G	Reference e-cigarette	Closed tank	Tobacco	3.0 w/w%	*ad libitum*, 5 min use

◆ **Plasma nicotine analysis**

14 venous blood samples taken at –5, 1, 3, 5, 7, 10, 15, 30, 45, 60, 90, 120, 180, and 360 min

◆ **Nicotine consumption**

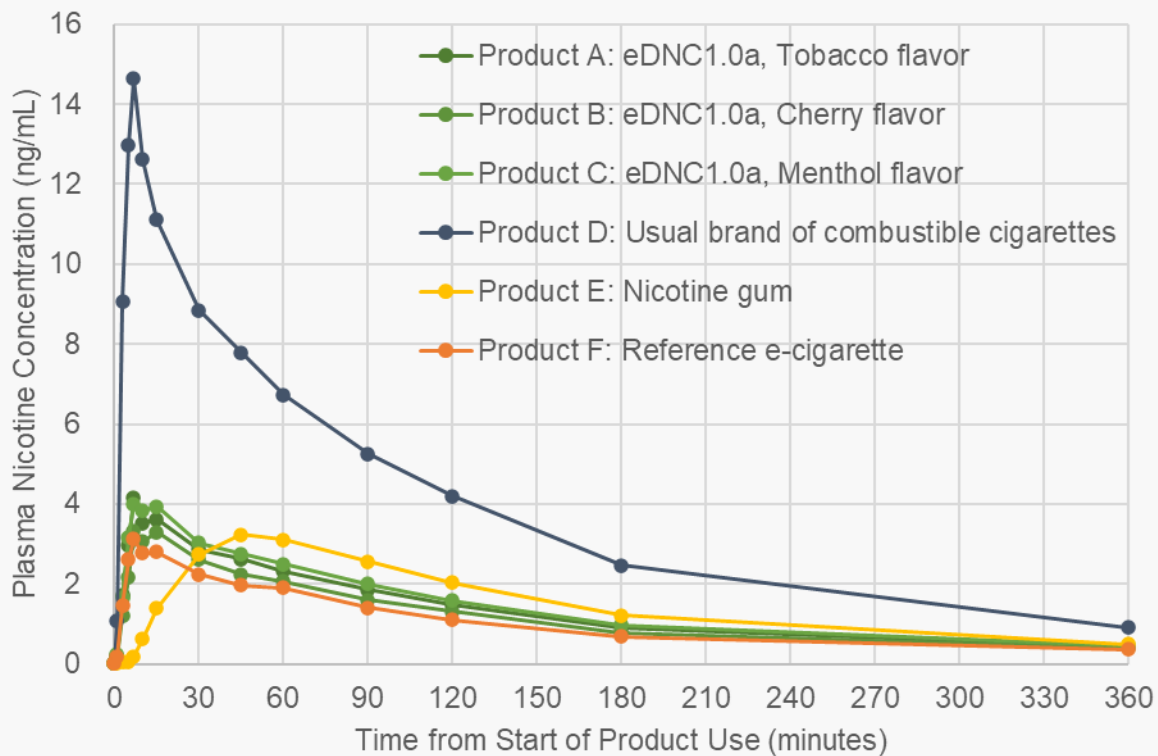Estimated from the nicotine content (w/w%) of the e-liquid and weight loss of product following product use.

◆ **Subjective effects measures**

Three questionnaires were administered after product use: the product liking VAS questionnaire, the Intent to Use Again VAS questionnaire, and the modified Product Evaluation Scale (mPES) questionnaire
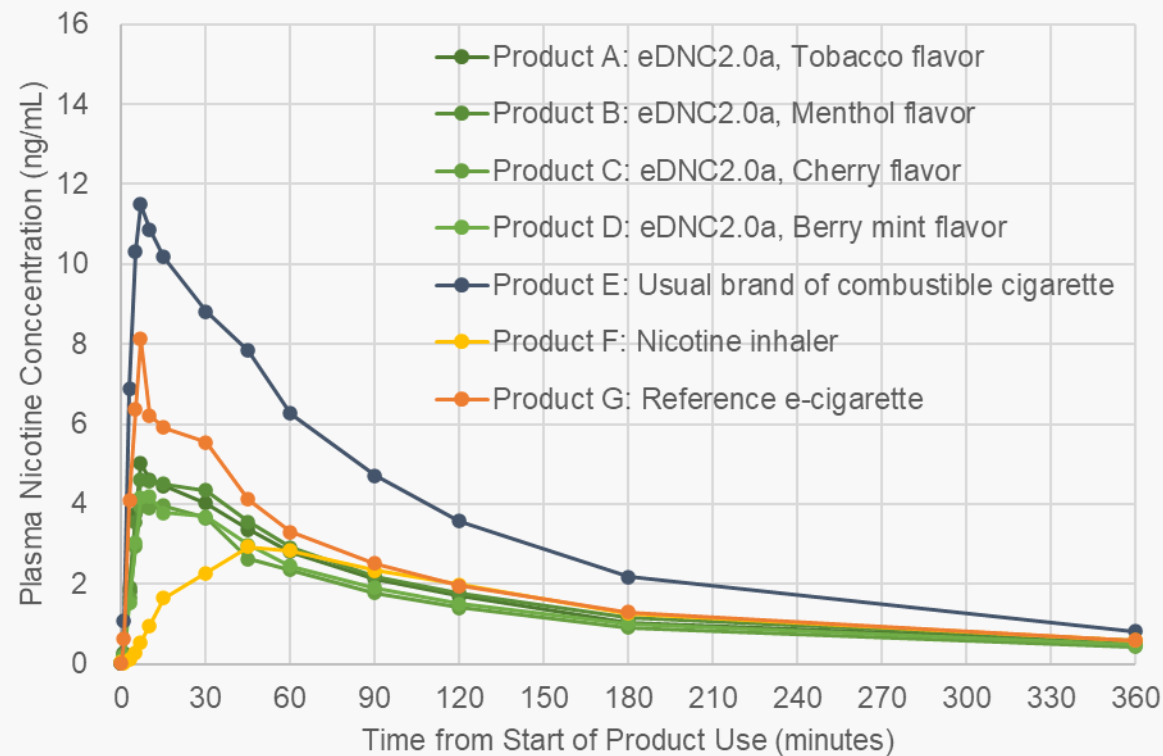
Profiles of Plasma Nicotine Concentration

- The profile of plasma nicotine concentration-time curves obtained after use of test e-cigarettes with different flavor variants was similar, in each study.

- Plasma nicotine concentrations following use of all test e-cigarettes were lower throughout the 360-minute sampling period than those following use of CC, in both studies.

Study 1 (n = 52)

Legend:
- Product A: eDNC1.0a, Tobacco flavor
- Product B: eDNC1.0a, Cherry flavor
- Product C: eDNC1.0a, Menthol flavor
- Product D: Usual brand of combustible cigarettes
- Product E: Nicotine gum
- Product F: Reference e-cigarette

Y-axis: Plasma Nicotine Concentration (ng/mL)
X-axis: Time from Start of Product Use (minutes)

Study 2 (n = 51)

Legend:
- Product A: eDNC2.0a, Tobacco flavor
- Product B: eDNC2.0a, Menthol flavor
- Product C: eDNC2.0a, Cherry flavor
- Product D: eDNC2.0a, Berry mint flavor
- Product E: Usual brand of combustible cigarette
- Product F: Nicotine inhaler
- Product G: Reference e-cigarette

Y-axis: Plasma Nicotine Conccentration (ng/mL)
X-axis: Time from Start of Product Use (minutes)

Nicotine PK Parameters and Consumption

- Any test e-cigarettes were characterized by slower Tmax, and statistical significantly lower AUC_{0-last} and C_{max} compared to CC, in both studies.

- The mean of nicotine consumption differed very little between test e-cigarettes with flavor variants, in each study.

| Study	Product	Nicotine consumption (mg) Mean (SD)	C_{max} (ng/mL) GLS mean (95% CI)*	AUC_{0-last} (ng*hr/mL) GLS mean (95% CI)*	T_{max} (min) Median (min, max)
Study 1 (n = 52)	Product A: eDNC1.0a, Tobacco flavor	**0.75** (0.39)	**3.71**[†] (3.15, 4.37)	**6.24**[†] (5.37, 7.25)	**15** (5.0, 60)
	Product B: eDNC1.0a, Cherry flavor	**0.71** (0.32)	**3.44**[†] (2.92, 4.05)	**5.62**[†] (4.84, 6.54)	**15** (7.0, 45)
	Product C: eDNC1.0a, Menthol flavor	**0.84** (0.47)	**4.18**[†] (3.55, 4.92)	**7.04**[†] (6.06, 8.18)	**15** (5.0, 60)
	Product D: Combustible cigarettes	N/A	**15.3** (13.0, 18.0)	**21.1** (18.2, 24.5)	**7.1** (3.0, 45)
	Product E: Nicotine gum	N/A	**3.26** (2.77, 3.85)	**8.21** (7.06, 9.54)	**45** (30.0, 90)
	Product F: Reference e-cigarette	**0.68** (0.40)	**2.90** (2.46, 3.42)	**4.64** (3.99, 5.39)	**15** (5.0, 60)
Study 2 (n = 51)	Product A: eDNC2.0a, Tobacco flavor	**1.05** (0.60)	**4.22**[†] (3.35, 5.31)	**6.71**[†] (5.14, 8.78)	**10** (5.0, 41)
	Product B: eDNC2.0a, Menthol flavor	**1.09** (0.62)	**4.11**[†] (3.27, 5.18)	**6.62**[†] (5.06, 8.66)	**10** (3.0, 61)
	Product C: eDNC2.0a, Cherry flavor	**0.93** (0.53)	**3.52**[†] (2.80, 4.44)	**5.28**[†] (4.04, 6.90)	**15** (5.0, 60)
	Product D: eDNC2.0a, Berry mint flavor	**0.96** (0.59)	**3.99**[†] (3.16, 5.03)	**6.17**[†] (4.71, 8.08)	**10** (5.0, 40)
	Product E: Combustible cigarettes	N/A	**12.3** (9.76, 15.5)	**19.0** (14.6, 24.9)	**7.3** (3.0, 40)
	Product F: Nicotine inhaler	N/A	**1.95** (1.55, 2.46)	**3.93** (3.00, 5.15)	**40** (7.0, 90)
	Product G: Reference e-cigarette	**1.45** (0.90)	**5.74** (4.55, 7.22)	**7.69** (5.88, 10.1)	**7.0** (3.0, 40)

GLS means were evaluated separately in a linear mixed-effects ANOVA model with fixed effects for period, sequence, product, and a random effect for subject nested within sequence.

† Significantly different from usual brand of combustible cigarettes (Product D in Study 1, Product E in Study 2); $p < 0.05$.

Subjective Effects Measures

- Overall product liking, intent to use the product again, and subscales of mPES were markedly lower when using any test e-cigarettes compared to CC.

Study	Product	Liking VAS > 50 mm - n (%)	Intent to Use Again VAS > 50 mm - n (%)
Study 1 (n = 52)	Product A: eDNC1.0a, Tobacco flavor	32 (**61.5%**)	36 (**69.2%**)
	Product B: eDNC1.0a, Cherry flavor	32 (**61.5%**)	31 (**59.6%**)
	Product C: eDNC1.0a, Menthol flavor	33 (**63.5%**)	32 (**61.5%**)
	Product D: Combustible cigarettes	47 (**90.4%**)	51 (**98.1%**)
	Product E: Nicotine gum	30 (**57.7%**)	29 (**55.8%**)
	Product F: Reference e-cigarette	36 (**69.2%**)	31 (**59.6%**)
Study 2 (n = 51)	Product A: eDNC2.0a, Tobacco flavor	16 (**32.0%**)	31 (**62.0%**)
	Product B: eDNC2.0a, Menthol flavor	27 (**52.9%**)	34 (**66.7%**)
	Product C: eDNC2.0a, Cherry flavor	26 (**51.0%**)	39 (**76.5%**)
	Product D: eDNC2.0a, Berry mint flavor	30 (**58.8%**)	32 (**62.7%**)
	Product E: Combustible cigarettes	45 (**88.2%**)	48 (**94.1%**)
	Product F: Nicotine inhaler	16 (**31.4%**)	16 (**31.4%**)
	Product G: Reference e-cigarette	32 (**62.7%**)	43 (**84.3%**)
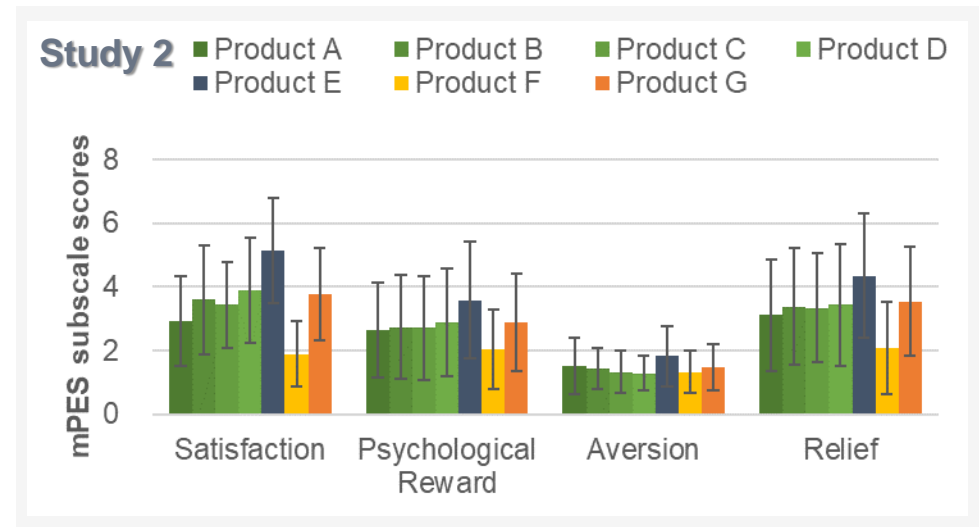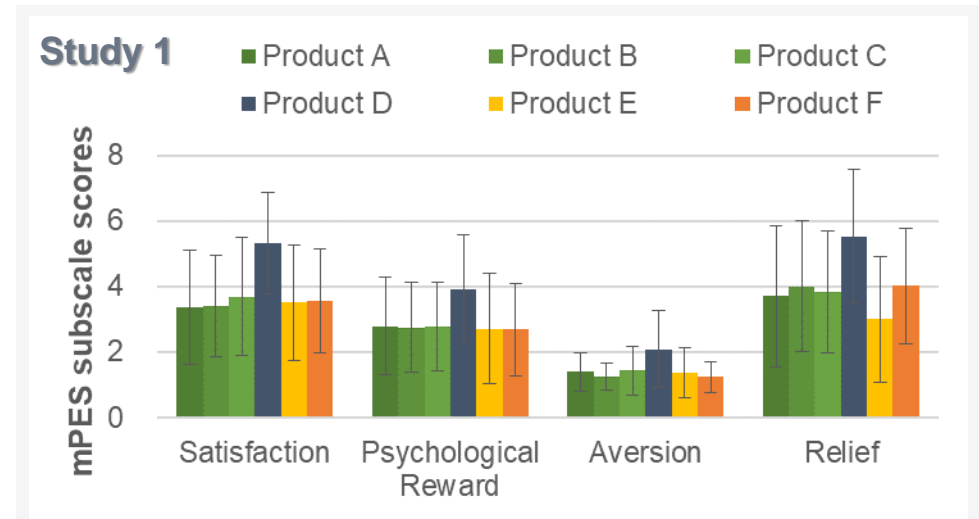
Product Liking VAS: Questionnaire ("Do you like the product effect?") rating scales with "Not at all (0 mm)" to "Extremely (100 mm)".
Intent to Use Product Again VAS: Questionnaire ("If given the opportunity, would you use this product again?") rating scales with "Definitely Would Not (0 mm)" to "Definitely Would (100 mm)".
The subscales of modified Product Evaluation Scale (mPES): Each item was rated on a 7-point Likert scale ranging from 1 ("Not at all") to 7 ("Extremely"). [9]

EXPLORATORY INVESTIGATION

Exploratory Analysis – Consumption vs. AUC/Cmax

- Although the mean values of nicotine consumption differed very little between e-cigarettes, the ranking of nicotine consumption generally reflected the ranking of AUC_{0-last} and C_{max} values in each study.

Study	Product	Nicotine consumption (mg) Mean (SD)	C_{max} (ng/mL) GLS mean (95% CI)*	AUC_{0-last} (ng*hr/mL) GLS mean (95% CI)*	T_{max} (min) Median (min, max)
Study 1 (n = 52)	Product F: Reference e-cigarette	0.68 (0.40)	2.90 (2.46, 3.42)	4.64 (3.99, 5.39)	15 (5.0, 60)
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	Product G: Reference e-cigarette	1.45 (0.90)	5.74 (4.55, 7.22)	7.69 (5.88, 10.1)	7.0 (3.0, 40)

blue arrows "<" mean the ranking of nicotine consumption reflected the ranking of AUC_{0-last} and C_{max} values;
red arrows "<" mean the ranking of nicotine consumption did not reflect the ranking of AUC_{0-last} and C_{max} values

Exploratory Analysis – Consumption vs. AUC/Cmax

- It was concluded that the dose-response relationship was generally consistent across studies, and there was a good linear (R^2 = 0.695 and 0.555, respectively) relationship between estimated nicotine consumption and $AUC_{0\text{-last}}$ and C_{max} values.
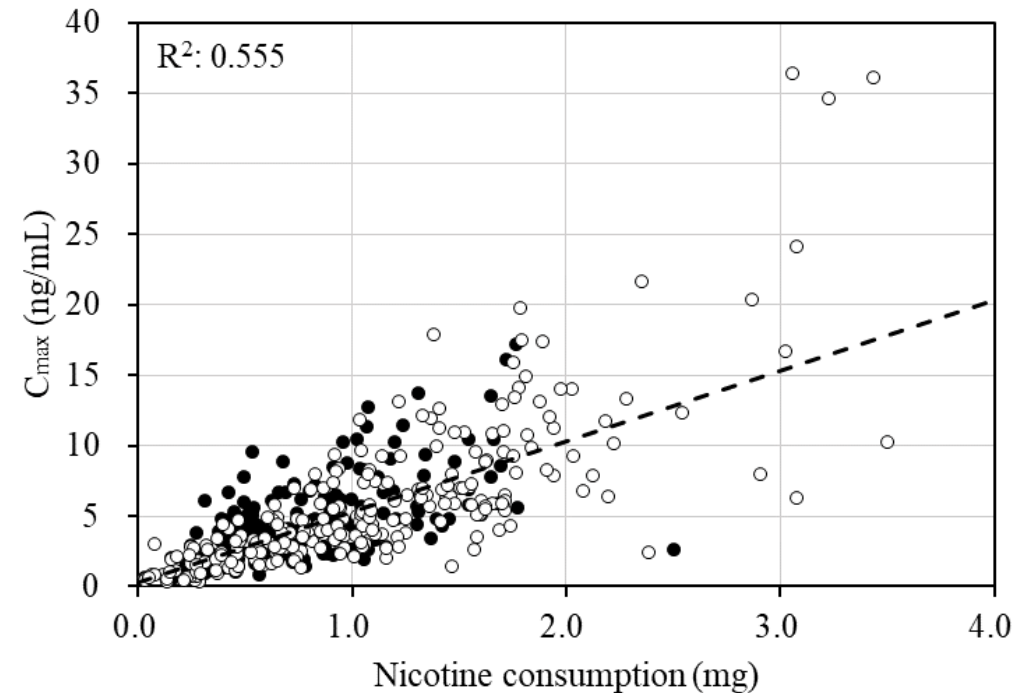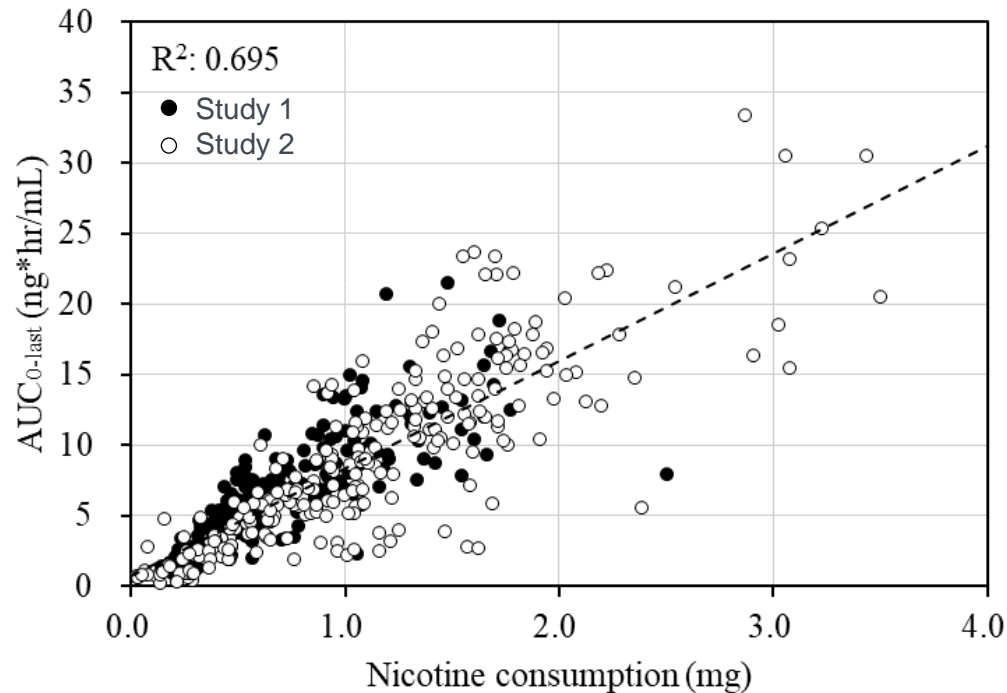
Dotted lines show the fixed effects regression between $AUC_{0\text{-last}}$ or C_{max} and estimated nicotine consumption derived from a linear mixed-model that adjusted the intercepts and slopes by study. R^2 indicates the coefficient of determination derived from a simple linear regression (crude regression) taking into account all data from the two studies.

Exploratory Analysis – Consumption vs. AUC/Cmax

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Published data - mean of Cmax and nicotine consumption of other e-cigarettes (◆JUUL [10,11]; ◆VUSE [12])
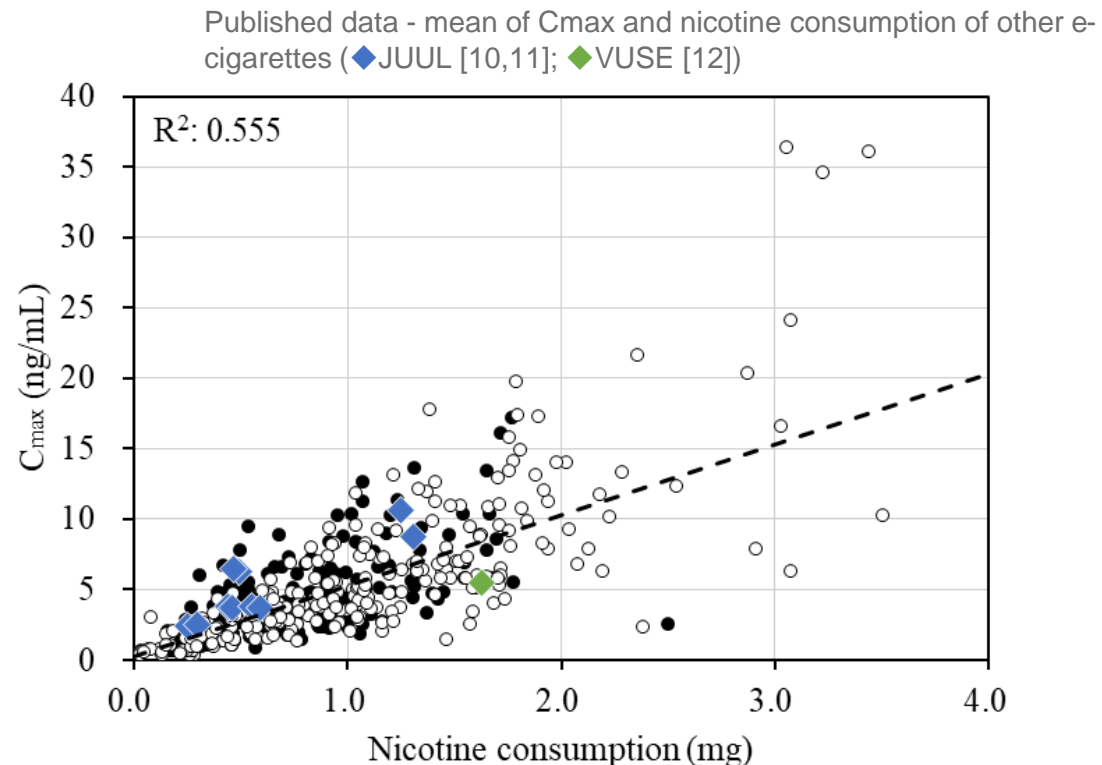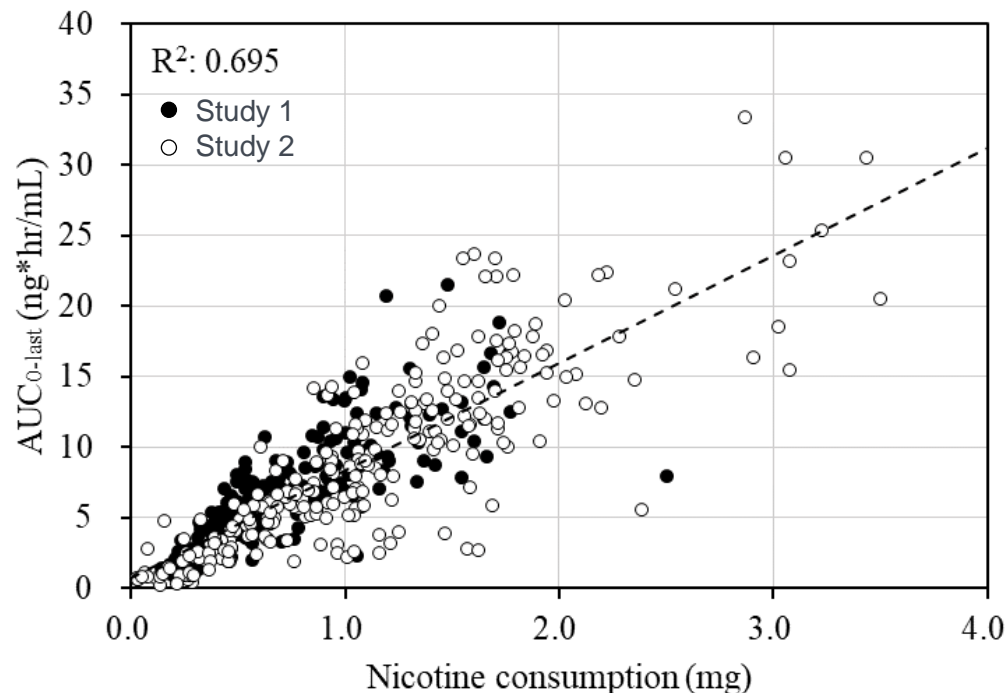
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SUMMARY

Summary

- Nicotine exposure from cig-a-like e-cigarette (eDNC1.0a) with three flavor variants and closed tank e-cigarette (eDNC2.0a) with four flavor variants was less than that from CC but similar to or greater than that from pharmaceutical nicotine replacement products.

- Overall, the use of cig-a-like e-cigarette (eDNC1.0a) with three flavor variants and closed tank e-cigarette (eDNC2.0a) with four flavor variants by cigarette smokers resulted in responses to subjective effects questionnaires that were lower than those obtained for the usual brand of CC but similar or greater than pharmaceutical nicotine replacement products.

- Furthermore, linear relationships were found between estimated nicotine consumption and plasma nicotine PK parameters following e-cigarette use. Our findings indicate that nicotine PK determination following e-cigarette use can be estimated by non-invasive examination of consumption through human use and provide additional insights to clinical PK studies.

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