Exhaled Breath Levels of Selected Constituents From Controlled Use of MarkTen® e-Vapor Products in Adult e-Vapor Users

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Abstract

Introduction: Few reports exist of exhaled breath levels of constituents during use of e-vapor products (EVPs). MarkTen® EVPs look similar to combustible cigarettes and consist of a battery and replaceable cartridges that contain propylene glycol (PG), glycerin (G), water, flavors and USP-grade tobacco-derived nicotine. The purpose of this study was to characterize the levels of selected constituents in exhaled breath during use of MarkTen® EVP.

Method: EVP users (n=32, 56% male) were randomized to use one of four flavor varieties each day for 4 days (2 menthol and 2 non-menthol flavors delivering 0.13 mg to 0.23 mg nicotine per machine measured 5 s puff). Subjects were instructed to take 10 puffs from each EVP using 5 s puff durations with 30 s inter puff intervals. The collection was performed once with a "sham" device (inactive battery + empty cartridge) and then again with the study EVP. Exhaled breath was collected after the first puff until 1 min after the last puff using a mouthpiece filter with a cryogenic condensation collection tube system. The collections were analyzed for PG, G, nicotine, menthol, formaldehyde, acrolein and acetaldehyde.

Results: Sham corrected exhaled breath levels (ANCOVA Least Square Means/10 puffs) across the flavor varieties ranged from: 1199.7 to 3354.5 µg for PG, 5366.8 to 6484.7 µg for G; 89.4 to 195.7 µg for nicotine, 0.17 (non-menthol product) to 31.01 µg (menthol product) for menthol, and from 0.25 to 0.34 µg for formaldehyde. Inter-subject variability was high for these analytes, with the largest range occurring for G where individual values ranged from 0 to 20,645 µg/10 puff sample. All acrolein and acetaldehyde exhaled breath measurements were below the detection limits. E-liquid consumption (cartridge weight change) during the 10 puff collections ranged from 34 to 41 mg across the four products.

Conclusions: Detectable levels of PG, G, nicotine, menthol and formaldehyde are present in exhaled breath during use of EVPs. These values are currently being used in computational models to estimate room air levels under different room and use conditions.

Purpose & Objective

Purpose: In Section VI (H) (2b) of the Draft Guidance for Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems (May 2016), the FDA recommends that applications:

> "should provide data that adequately characterizes the likely impact of the new tobacco product on the health of both users and nonusers of tobacco products in order to support that marketing the new tobacco product would be appropriate for the protection of the public health."

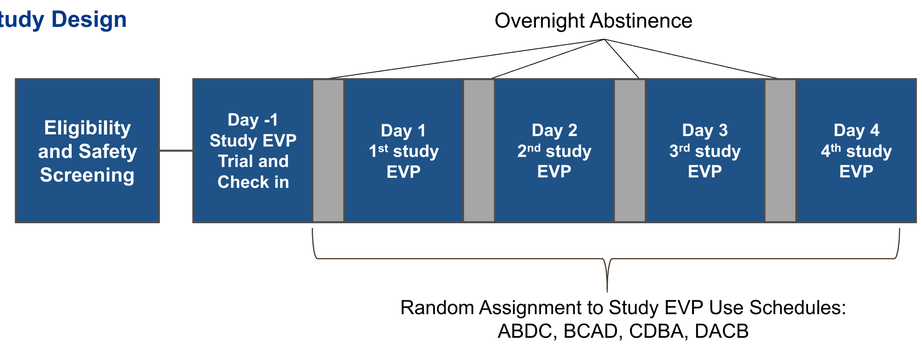
The purpose of this study was to characterize the levels of selected constituents in the exhaled breath during use of the study EVPs. The results of this study will support our assessment of the likely impact of the EVPs on the health of non-users utilizing computational modeling to estimate the potential room air levels under different room and use conditions. The modeling results are presented at SRNT 2018, Poster 190 (Session 5) "Estimation of Second Hand Exposure Levels from ENDS and Conventional Cigarette Use Using Computational Modeling."

Objective: The primary objective of this study was to estimate the change in total amount of nicotine, glycerin, propylene glycol, menthol, formaldehyde, acetaldehyde, and acrolein in exhaled breath samples between sham (inactive battery and empty cartridge) and controlled product use for four EVPs.

Methods

- Adult, generally healthy EVP users (at least 3 months of use and used at least 4 out of the past 7 days, n=32, 56% male) who were willing to use all four study EVPs after product trial at Day -1 were randomized to use one of four MarkTen® EVPs each day for 4 days (Figure 1). This study was conducted in compliance with the International Conference on Harmonisation Harmonized (ICH) Tripartite Guideline regarding Good Clinical Practice (GCP). All pertinent study documents, including the protocol, were reviewed and approved by the Chesapeake Institutional Review Board (IRB) prior to study initiation. All participants reviewed, signed, and dated the IRB approved Informed Consent Form before participation in this study.

Figure 1. Study Design

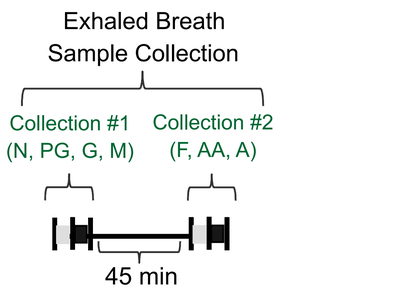


On Days 1 through 4, 32 participants used 1 study EVP for exhaled breath assessments (Figure 2). After exhaled breath collections each day, participants were allowed to use the study EVP ad libitum for 12 h for puff topography assessment (data not shown).

- On the morning of each study day, subjects were instructed to take 10 puffs from each product using 5 s puff durations with 30 s inter puff intervals. The collection was performed once with a "sham" device (inactive battery + empty cartridge) and then again with the study EVP. The sham and study EVP collections were conducted twice, once for N, G, PG, and M and then a second collection was performed 45 min later for F, AA, and A collections (Figure 2a).
- Exhaled breath was collected from the first puff until 1 min after the last puff using a mouthpiece filter with a cryogenic condensation collection tube system (RTube™ RT, Figure 2b).
  - The filter for Trapping Container #1 (N, G, PG, M collection) consisted of one 50 mm AirLife Bacterial/Viral filter housed in a plastic filter holder before the RTube™ RT.
  - The filter for Trapping Container #2 (F, AA, A collection) consisted of two 50mm AirLife Bacterial/Viral filter housed in a plastic filter holder treated with 2,4-dinitrophenylhydrazine before the RTube™ RT.
  - Exhaled breath collections were done over a set time period with no assessment of potential differences in exhaled breath volume.
  - Collections and analysis performed by Enthalpy Analytical, Inc., Durham, NC. Collections methods were verified to capture >90% of analytes compared to ISO machine smoking collections.
  - Linear mixed model for analysis of covariance (ANCOVA) was fitted separately for each analyte. In the model, the response variable was sham-corrected analyte amount, study EVP, period and sequence were the fixed effects, sham sample analyte level was the covariate and subject nested within sequence was the random effect.

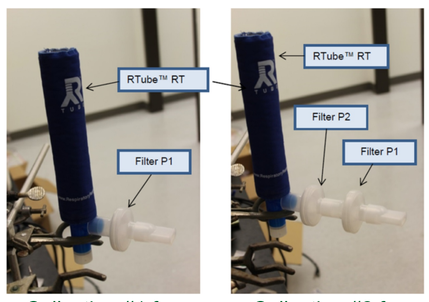
Figure 2. Exhaled Breath Sample Collection

(a)



- Sham Sample Collections: 10 puffs of 5 sec duration
- Study EVP Sample Collections: 10 puffs of 5 sec duration

(b)



Collection #1 for: Nicotine, PG, Glycerin, and Menthol

Collection #2 for: Formaldehyde, Acetaldehyde, and Acrolein

e-Vapor Products

- **MarkTen® A** 2.5% nicotine by weight
- **MarkTen® B** 4.0% nicotine by weight
- **MarkTen® C** 3.5% nicotine by weight, Menthol
- **MarkTen® D** 4.0% nicotine by weight, Menthol

Constituents Investigated

- **Nicotine** (N)
- **Propylene glycol** (PG)
- **Formaldehyde** (F)
- **Acrolein** (A)
- **Glycerin** (G)
- **Menthol** (M)
- **Acetaldehyde** (AA)

Study Population

Age	Mean	36.7
	Range	23-62
Gender	Male	18 (56%)
	Female	14 (44%)
Race	White or Caucasian	9 (28%)
	Black or African American	22 (69%)
	Other	1 (3%)
Current EVP type	Disposable / Cartridge based	11 (34%)
	Refillable	17 (53%)
	Disposable / Cartridge based + Refillable	4 (13%)
EVP use in the past week	Mean	6.5 days
	Range	4-7 days

Study EVP Aerosol Characterization*

EVP	Menthol (mg/puff) (SD)	Nicotine (mg/puff) (SD)	Glycerin (mg/puff) (SD)	Propylene Glycol (mg/puff) (SD)	Cartridge Weight Change (mg/puff) (SD)
MarkTen A	BLOQ	0.126 (0.006)	2.521 (0.123)	1.470 (0.074)	5.267 (0.222)
MarkTen B	BLOQ	0.201 (0.013)	2.885 (0.097)	1.011 (0.042)	5.275 (0.329)
MarkTen C	0.081 (0.003)	0.187 (0.005)	2.240 (0.075)	1.986 (0.070)	5.588 (0.177)
MarkTen D	0.130 (0.014)	0.232 (0.024)	2.294 (0.311)	1.940 (0.245)	5.972 (0.603)

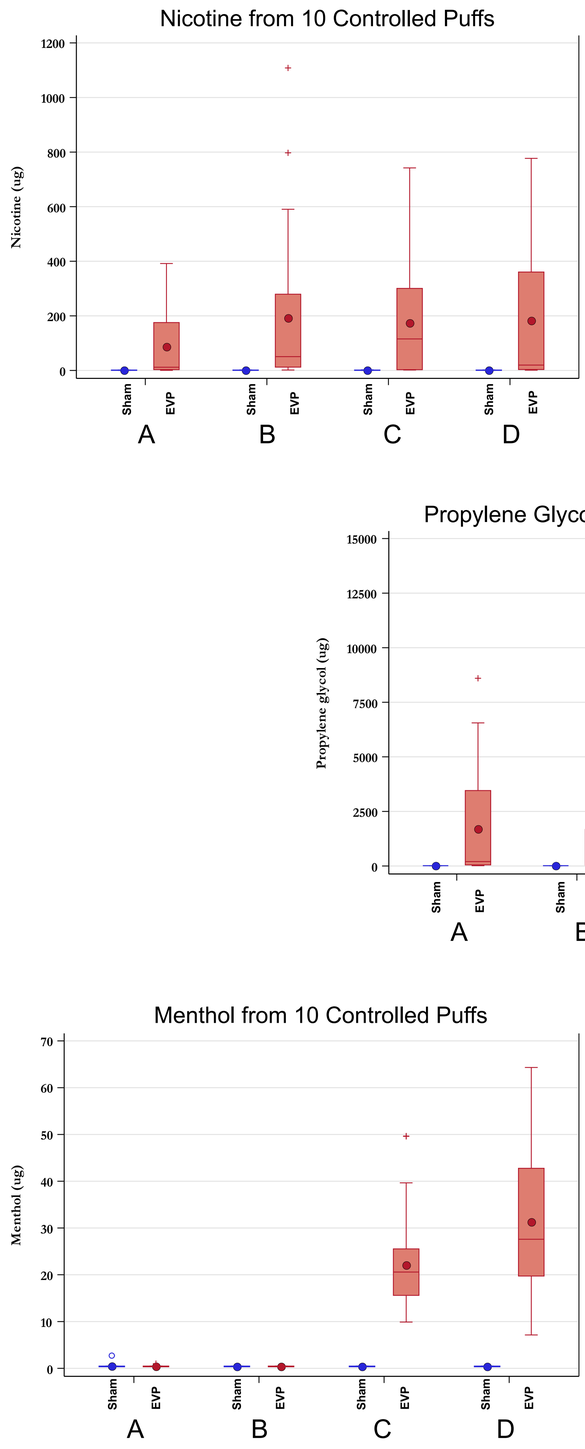
EVP	Formaldehyde (µg/puff) (SD)	Acetaldehyde (µg/puff) (SD)	Acrolein (µg/puff) (SD)	Cartridge Weight Change (µg/puff) (SD)
MarkTen A	0.100 (0.029)	0.065 (0.008)	BLOQ	5.662 (0.383)
MarkTen B	0.178 (0.017)	0.090 (0.008)	BLOQ	5.362 (0.314)
MarkTen C	0.187 (0.113)	0.075 (0.048)	BLOQ	5.603 (0.458)
MarkTen D	0.133 (0.023)	0.051 (0.006)	BLOQ	6.088 (0.372)

*Aerosol collected under 55 cc volume, 5 s duration, 30 s interval parameters by ALCS (20 puff collection), all values were background subtracted. No characterization was done for sham devices.

Results

Sham and Study EVP Exhaled Breath

- Levels below minimum detection limit were set to the minimum detection limit.
- Outliers (open circles, plus signs)
- Means are represented by the closed circles; first quartiles are represented by the bottom of the boxes; medians are represented by the line within the boxes; third quartiles are represented by the top of the boxes; 1.5 times the first and third quartiles are represented by the lines extending below and above the boxes, respectively.



ANCOVA Least Square Means (95% CI) of Sham Corrected Exhaled Breath from 10 Controlled Puffs

Study EVP	Nicotine [µg]	Glycerin [µg]	Propylene Glycol [µg]	Menthol [µg]	Formaldehyde [µg]
A	**89.44** (15.77, 163.11)	**5972.3** (4191.1, 7753.6)	**1678.4** (592.14, 2764.6)	**0.17** (–2.92, 3.25)	**0.25** (0.12, 0.38)
B	**195.70** (122.01, 269.38)	**6099.5** (4317.8, 7881.2)	**1199.7** (113.74, 2285.7)	**0.35** (–2.70, 3.40)	**0.25** (0.12, 0.38)
C	**168.83** (95.17, 242.50)	**6484.7** (4701.7, 8267.6)	**3354.5** (2266.6, 4442.3)	**21.11** (18.06, 24.16)	**0.34** (0.21, 0.47)
D	**182.65** (108.63, 256.67)	**5366.8** (3575.9, 7157.7)	**2511.0** (1416.1, 3605.9)	**31.01** (27.91,34.12)	**0.30** (0.17, 0.43)

Estimated Mean e-Liquid Consumed* During Exhaled Breath Collections

Study EVP		A	B	C	D
	Sample Size	32	32	32	32
Collection #1	Mean (mg)	**35**	**34**	**40**	**37**
(N, G, PG, M)	SD	8.7	11.4	12.6	12.3
Collection #2	Mean (mg)	**36**	**36**	**41**	**38**
(F, AA, A)	SD	11.5	11.9	14.6	12.4

*Cartridge weight change over the 10 puff session

Estimated Amount of Constituent Exhaled per mg e-Liquid Consumed*

Study EVP	Nicotine: µg exhaled / mg cartridge weight change	Glycerin: µg exhaled / mg cartridge weight change	PG: µg exhaled / mg cartridge weight change	Menthol: µg exhaled / mg cartridge weight change	Formaldehyde: µg exhaled / mg cartridge weight change
A	2.56	170.64	47.95	-	0.0069
B	5.76	179.40	35.29	-	0.0069
C	4.22	162.12	83.86	0.53	0.0083
D	4.94	145.05	67.86	0.84	0.0079

*Exhaled breath values from statistical model results and e-liquid consumption from cartridge weight change over the 10 puff session

Conclusion

- The measured constituents in exhaled breath samples during study EVP use are highly variable.
- Nicotine, Glycerin, PG and Formaldehyde were detected in the exhaled breath for all four study EVPs. Menthol was detected in two menthol products.
- Acetaldehyde and Acrolein were below the detectable limit in exhaled breath during use of any of the four study EVPs.
- These values are currently being used in computational models to estimate room air levels under different room and use conditions.